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What counts in the brain?

The neural correlates of arithmetic in adults and children with and without learning disorders

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What counts in the brain: The neural correlates of arithmetic in adults and children with and without learning disorders

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Arithmetic constitutes a large part of our daily lives, yet its neural basis in adults and children with and without learning disorders is not yet fully understood. Neuroimaging research in adults has been mainly performed against the background of one theoretical framework: the Triple Code Model. This model acknowledges the influence of three codes, each with its own neural component: the magnitude code, located in the posterior parietal areas, is involved in estimating and comparing numerical magnitudes. The verbal code, which is localized in the left perisylvian areas, is implicated in the phonological processing of numbers. Finally, the visual code plays a role in the visual processing of Arabic digits. Although the former two codes have been extensively researched, research on the role and the anatomical location of the visual code has been scarce to date. Using univariate and multivariate analyses, an fMRI study in adults revealed no focal region specifically hosting the visual code, yet that digits were represented as distributed patterns.

The Triple Code Model was based on research in adults, and is therefore not simply transferable to children. Neuroimaging research on arithmetic in children is relatively scare to date and has often focused on investigating the neural correlates of various strategies children use to solve arithmetic problems. However, these previous studies have been confounded by the use of, for example, different operations. An fMRI study in typically developing children in which we manipulated presentation format rather than operation, indicated that children used procedural strategies when they were asked to perform non-symbolic subtractions, yet retrieved the solution from long term memory for symbolic subtractions. This study showed that neural strategy effects are not solely reliant on operation effects, but that they are dependent on the individual characteristics of arithmetic problems.

Despite the large role of arithmetic in everyday life, around one in ten children suffers from deficits in arithmetic processing (i.e., dyscalculia). Even more, children with reading disabilities (i.e., dyslexia) often show impairments in arithmetic as well. It remains however unclear if these comparable difficulties with performing arithmetic at the behavioral level, originate from similar neurobiological effects in dyscalculia and dyslexia. In an fMRI study in children with dyscalculia, children with dyslexia, children with comorbid dyslexia/dyscalculia and age-matched typically developing children, we found, using univariate analyses, hypo-activation for all children with learning disorders compared to typically developing children. Furthermore, no brain regions were significantly more activated during arithmetic in children with dyscalculia compared to children with dyslexia, and vice versa. To rule out the possibility that power issues drove this null-effect, we used multivariate analyses that indicated that, despite clear differences in their behavioral profiles, all children with learning disorders were remarkably similar in terms of their neural profiles.

Collectively, these studies and the univariate and multivariate analysis techniques that were used, helped us gain more insight into what counts in the brain during arithmetic processing.

Lien Peters
Wat telt in de hersenen: de neurale correlaten van rekenen in volwassenen en kinderen met en zonder leerstoornissen
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Rekenen is inherent aan ons dagelijkse leven. De neurale correlaten van rekenen bij volwassenen en kinderen met en zonder leerstoornissen zijn echter nog niet volledig duidelijk. Neurowetenschappelijk onderzoek bij volwassen kaderde tot hiertoe binnen het Triple Code Model. Dit model gaat uit van de invloed van drie codes met elk een eigen neurale component: de magnitudecode, gelokaliseerd in de posterieure pariëtale cortex, is betrokken bij het schatten en vergelijken van numerieke grootheden. De verbale code, die in de linker perisylvische gebieden ligt, is betrokken bij de fonologische representatie van hoeveelheden. De visuele code ten slotte, speelt een rol bij de visuele verwerking van Arabische cijfers. Terwijl de neurale correlaten van de magnitude- en verbale codes al uitgebreid werden onderzocht, werd slechts in beperkte mate onderzoek gevoerd naar de rol en de anatomische locatie van de visuele code. Met behulp van univariate en multivariate analyses heeft een fMRI-studie bij volwassenen aangetoond dat de visuele code niet in een specifiek gebied gelokaliseerd is, maar dat cijfers worden verwerkt in termen van neurale patronen.
Het Triple Code Model is gebaseerd op onderzoek bij volwassen en is bijgevolg niet zomaar bruikbaar bij kinderen. Tot nog toe werd bij kinderen slechts in beperkte mate neurowetenschappelijk onderzoek naar rekenen gevoerd, en dit onderzoek was vaak gericht op de neurale correlaten van verschillende strategieën die kinderen gebruiken om rekenproblemen op te lossen. Deze studies zijn echter vertekend, bijvoorbeeld door gebruik van verschillende operaties. Een fMRI-studie bij normaal ontwikkelende kinderen, waarbij we de presentatievorm en niet de operatie manipuleerden, toonde aan dat kinderen voor het oplossen van non-symbolische aftrekoefeningen gebruik maken van procedurele strategieën, maar dat ze voor het oplossen van symbolische aftrekoefeningen rekenfeiten ophalen uit het langetermijngeheugen. Deze studie demonstreerde dat neurale strategie-effecten niet louter afhangen van het effect van wiskundige operaties, maar ook van de individuele kenmerken van het rekenprobleem in kwestie.
Het belang van rekenen in het dagelijkse leven hoeft geen betoog, maar ongeveer één kind op tien kampt met dyscalculie. Kinderen met dyslexie vertonen daarnaast vaak ook problemen met het ophalen van rekenfeiten. Het is echter onduidelijk of deze gelijkaardige leerproblemen op gedragsniveau het resultaat zijn van gelijkaardige neurobiologische effecten in dyscalculie en dyslexie. Uit een fMRI-studie bij kinderen met dyscalculie, met dyslexie, met co-morbide dyslexie/dyscalculie en met typische ontwikkeling bleek dat kinderen met een leerstoornis tijdens een rekentaak lagere neurale activiteit vertoonden dan typisch ontwikkelende kinderen. Verder werden geen neurale gebieden gevonden die meer werden geactiveerd bij kinderen met dyscalculie dan bij kinderen met dyslexie, en vice versa. Om uit te sluiten dat dit nulresultaat te wijten is aan een gebrek aan onderscheidingsvermogen, gebruikten we multivariate analyses. Deze toonden aan dat kinderen met leerstoornissen opmerkelijke gelijkenissen toonden op neuraal vlak, ondanks het grote verschil op gedragsmatig niveau.

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CHAPTER 1

General introduction & aims

We deal with numbers and arithmetic on a daily basis. We set dates and times for meetings, adjust our speed during driving, calculate our new arriving hour when the train is delayed and adjust recipes for the appropriate number of people. This numerical information can be presented to us in various formats. Not only can we count or estimate a number of objects presented to us (i.e., non-symbolic format), we also use socially devised, symbolic formats such as number words and Arabic digits. Very young, we learn that “three”, "3", and "•••" all represent the same number, and we are taught to calculate using these three formats: We initially learn arithmetic by counting the number of objects (non-symbolic; e.g., we learn addition by counting the number of apples from two piles), and later on we learn that these arithmetic exercises can be solved in symbolic formats as well.

Our ability to efficiently process numerical information can have a great impact on our daily life. For example, Gerardi, Goette and Meier (2013) found that numerical ability predicts mortgage default, which can have profound effects on a person's life. Furthermore, children's ability to process numerical magnitudes is related to their mathematical achievement, and this effect is stronger for symbolic than for non-symbolic numerical magnitude processing (for a review, see De Smedt, Noël, Gilmore, & Ansari, 2013; for meta-analyses, see Fazio, Bailey, Thompson, & Siegler, 2014 and Schneider et al., 2016). Children with dyscalculia[1], who show persistent impairments in acquiring basic mathematical competencies, are known to have deficits in their ability to represent numerical magnitudes (Butterworth, Varma, & Laurillard, 2011; De Smedt et al., 2013; Noël & Rousselle, 2011). The representation of these numerical magnitudes is associated with and predictive of arithmetic fact mastery (Vanbinst, Ceulemans, Ghesquière, & De Smedt, 2015; Vanbinst, Ghesquière, & De Smedt, 2012), which is impaired in children with dyscalculia as well (Geary, 1993; Shalev & Gross-Tsur, 2001).
However, deficits in retrieving arithmetic facts are not only observed in children with dyscalculia. Children with dyslexia[1], who are specifically impaired in reading, also often show more difficulties in retrieving arithmetic facts compared to typically developing children (De Smedt & Boets, 2010; Evans, Flowers, Napoliello, Olulade, & Eden, 2014; Träff & Passolunghi, 2015). Additionally, the comorbidity between dyslexia and dyscalculia is rather high (around 40%; see Wilson et al., 2015), indicating that many children with a specific

[1] Throughout this dissertation, the term ‘dyscalculia’ should be interpreted as a learning disorder in which the pattern of behavioral deficits is focused around impairments in arithmetic, without impairments in reading. The term ‘dyslexia’ should be interpreted as a learning disorder in which the pattern of deficits is focused around impairments in reading, without impairments in arithmetic.

learning disorder (dyscalculia, dyslexia, or comorbid dyslexia/dyscalculia) show difficulties performing arithmetic.

Although specific learning disorders are categorized as neurodevelopmental disorders in the DSM-5 (American Psychiatric Association, 2013), the neurobiological origin of these learning disorders remains unclear to date. Furthermore, despite the high comorbidity between dyscalculia and dyslexia, no study to date has investigated if the neurological deficits associated with dyslexia and dyscalculia are specific, or if there are domain-general (neurological) processes affected in both learning disorders.

In the remainder of this introduction, the neural basis of numerical magnitude processing and arithmetic in adults and in children is discussed. Next, we present the existing literature on the neurological basis of arithmetic deficits in dyscalculia, dyslexia and comorbid dyslexia/dyscalculia. Finally, the techniques used throughout this thesis are described, and the aims of this doctoral dissertation are disclosed.

1.1 The neural correlates of arithmetic in adults

The most commonly used theoretical framework to study the neural basis of numerical magnitude processing and arithmetic is the Triple Code Model (Dehaene & Cohen, 1995, 1997). According to this model, three distinct codes of numerical information play a role while processing numbers (e.g., deciding which number is larger) or performing arithmetic. First, the *visual* code is involved in processing Arabic number forms, and in recognizing and discriminating number-letter strings. This process takes place in the inferior ventral occipito-temporal areas. Second, we have an analogue quantity or *magnitude* code which represents the semantic meaning of a number, allowing us to estimate and compare numerosities. This code is located in the parietal areas, more specifically in the intraparietal sulcus. Third, a *verbal* code is developed, in which numbers are represented by words or phonological codes. This code is located in the left-hemispheric perisylvian areas and in the left angular gyrus (Dehaene, Piazza, Pinel, & Cohen, 2003) and is implicated in retrieving arithmetic facts.

Dehaene and Cohen (1995, 1997) further proposed two routes through which arithmetic can take place. A *direct* route is taken when the solution can be retrieved from arithmetic facts stored in verbal long-term memory (verbal code), which is mostly the case for multiplication and small additions (see e.g., Grabner et al., 2009). The *indirect* route is followed when the solution to a problem cannot be directly retrieved from memory, and when semantically meaningful, procedural manipulations need to be performed (magnitude code), for example for more complex subtraction problems (as in 57 – 23). During procedural manipulations, the prefrontal cortex is recruited by enabling working memory and providing attentional resources (see e.g., Rivera, Reiss, Eckert, & Menon, 2005).

In their meta-analysis, Arsalidou and Taylor (2011) recommended to update this influential model based on the available imaging literature. They suggested to include the left putamen and claustrum in the model, as they are involved in cognitive processes such as the integration of information and the sequencing of input. Furthermore, they added the right angular gyrus, dorsolateral prefrontal cortex and frontopolar regions to the model, which play a role in visuo-spatial attention, monitoring and cognitive control, and computing mental calculations and sub-steps, respectively. Finally, the cingulate gyri, which are part of the error network, and the inferior frontal gyri, which play an important role in working memory and attentional processes, were suggested to be added to the model as well. Both numerical magnitude processing and arithmetic thus appear to recruit an extensive, neural network.

More recently, Menon (2015) described the neural network involved in arithmetic as consisting of five clusters (see Figure 1.1). A cluster comprising the primary visual cortex and the ventral temporal-occipital cortex is involved in number form processing (visual code). The intraparietal sulcus and superior parietal lobule process numerical quantity (magnitude code), whereas activity in the angular gyrus and medial and anterior temporal lobe is associated with episodic and verbal long-term memory (corresponding with the verbal code). Furthermore, the dorsolateral prefrontal cortex, basal ganglia, premotor cortex and supplementary motor area are recruited when working memory and cognitive control are involved. Finally, the anterior insula and ventrolateral prefrontal cortex play a role in salience and attentional control processes, which are mostly important when arithmetic exercises are solved using procedural strategies.

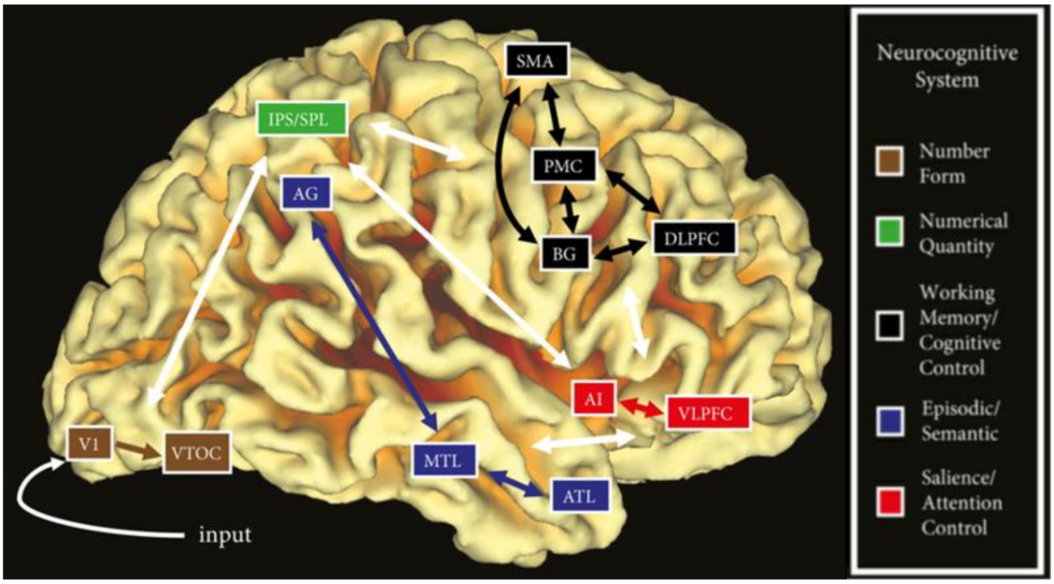

Figure 1.1. Diagram of the neural network involved in arithmetic (Menon, 2015; pp. 503).
Note. V1 = primary visual cortex, VTOC = ventral temporal-occipital cortex, IPS = intraparietal sulcus, SPL = superior parietal lobule, SMA = supplementary motor area, PMC = premotor cortex, DLPFC = dorsolateral prefrontal cortex, BG = basal ganglia, AG = angular gyrus, MTL = medial temporal lobe, ATL = anterior temporal lobe, AI = anterior insula, VLPFC = ventrolateral prefrontal cortex.

A substantial amount of (neuroimaging) research has focused on the specifics of the verbal and the magnitude code (see Ansari, 2008 for a review; Prado, Mutreja, & Booth, 2014): This research consistently indicates that the magnitude code is involved in numerical magnitude processing and in procedural strategies; The verbal code on the other hand comes into play once combinations of operands and solutions are stored into long-term memory (i.e., arithmetic facts). However, although areas in the ventral visual processing stream (e.g., lateral occipital cortex and fusiform gyrus; visual code) are consistently reported to be co-activated during arithmetic, with activity levels varying depending on arithmetic complexity (see Menon, 2015 for a review), the exact role and anatomical location of this visual code remains under-researched. Therefore, in ***Chapter 2***, we attempted to clarify the role and location of this visual code, by explicitly investigating the ventral visual processing stream in an arithmetic context.

These schematic overviews of the neural correlates of cognitive processes involved in arithmetic (Arsalidou & Taylor, 2011; Dehaene & Cohen, 1995; Menon, 2015) were all based on research in adults, and are not necessarily transferable to children (see e.g., Ansari, 2010).

With increasing age and schooling, there is a clear shift in strategies children use to solve arithmetic problems, from reliance on procedural strategies towards retrieving solutions from memory (Ashcraft, 1982; Geary, Widaman, Little, & Cormier, 1987). At the neural level, this shift is reflected in a shift from more engagement of the magnitude code in the intraparietal sulci and working memory in prefrontal cortex towards an increased reliance on the verbal code in the left perisylvian language-related areas, such as the angular gyrus (for a review, see Houdé, Rossi, Lubin, & Joliot, 2010; for a meta-analysis, see Kaufmann, Wood, Rubinsten, & Henik, 2011; Menon, 2015). These frontal-to-parietal and magnitude-to-verbal-code shifts have also been reported in the context of arithmetic training. As arithmetic proficiency increases (e.g., with arithmetic training), reliance on effortful procedural strategies makes way for increased reliance on arithmetic fact retrieval (see Zamarian, Ischebeck, & Delazer, 2009 for a review). Nonetheless, research on neural processes involved in numerical magnitude processing and arithmetic in children is relatively scarce and sometimes inconsistent, as we will elaborate below.

1.2 The neural correlates of arithmetic in typically developing children

Neuroimaging studies on numerical magnitude processing have consistently reported that a frontoparietal network is implicated in numerical magnitude processing tasks in typically developing children, with a key role in numerical magnitude processing for the intraparietal sulcus (for reviews, see Ansari, 2008; Houdé et al., 2010; Kaufmann et al., 2011). For example, Bugden, Price, McLean and Ansari (2012) found that brain activity during a symbolic number comparison task in the intraparietal sulcus was modulated by typically developing children’s mathematical competence: the higher the mathematical achievement score, the stronger the neural ratio effect (i.e., more precise and accurate representations of numbers).

Neuroimaging studies on arithmetic have consistently pointed towards the involvement of a whole brain network in children (see Kaufmann et al., 2011 and Menon, 2015 for a review): Posterior parietal areas (specifically the intraparietal sulcus) are thought to play a role in magnitude processing, language-related temporoparietal areas (e.g., superior temporal gyrus, angular gyrus and supramarginal gyrus) are implicated in storing and retrieving arithmetic facts, the prefrontal cortex plays a role in working memory and attentional processes, and ventral temporal cortex areas are associated with digit processing. Furthermore, a developmental, frontal-to-parietal shift in brain regions recruited during arithmetic has been repeatedly reported. Rivera, Reiss, Eckert and Menon (2005) investigated the brain activity of 8 to 19 year olds during single-digit additions and subtractions, and reported increased recruitment of left parietal areas (intraparietal sulcus and supramarginal gyrus) and lateral occipitotemporal cortex with age. Furthermore, they found decreased recruitment of prefrontal areas, indicating a decreased reliance on working memory and attentional processes with age. Rosenberg-Lee, Barth and Menon (2011) compared brain activation of 2nd and 3rd graders during single-digit additions. They found that 3rd graders recruited superior and inferior parietal areas, including angular gyrus, more than 2nd graders did, while the younger children showed higher activation levels in ventromedial prefrontal cortex. These findings indicated that even in the short time span of a year, a frontal-to-parietal shift in brain activity can already take place.

Previous studies have also investigated the development in strategies children use to solve arithmetic problems: from reliance on effortful procedural strategies (magnitude code) towards memory-based retrieval (verbal code). Prado et al. (2014) investigated the neural correlates of procedural strategies and fact retrieval in 8-13 year old children. These authors used a rhyming task to delineate left temporal, phonology and retrieval-related areas, and a non-symbolic number comparison task to localize the right superior parietal lobule and intraparietal sulcus, which are areas related to numerical magnitude processing and procedural strategies. These regions were subsequently used as regions of interest to investigate the neural difference between single-digit multiplication and subtraction. Prado et al. reported grade-related increases in the recruitment of these areas, at the expense of frontal activation. Furthermore, they reported that children recruited the number-related areas more for subtractions, yet the phonological areas more for multiplications. Prado et al. attributed these findings to subtractions being solved by using procedural strategies and multiplications by using fact retrieval. Finally, De Smedt, Holloway and Ansari (2011) reported higher activation levels in left medial temporal lobe and angular gyrus for smaller single-digit additions and subtractions (product of the operands was smaller than 25), but higher activation levels in the intraparietal sulcus for larger single-digit additions and subtractions (product of the operands larger than 25). Again, these findings were attributed to the strategies used to solve the problems: fact retrieval for small additions and subtractions, procedural strategies for large additions and subtractions.

The majority of neuroimaging studies on arithmetic in children have thus far focused on the recruitment of the magnitude code (procedural strategies) and verbal code (retrieval). Previous studies have investigated strategy use by presenting arithmetic problems in different operations (e.g., subtraction and multiplication in Prado et al., 2014), or of different problem sizes (e.g., small and large additions in De Smedt et al., 2011). This however creates a confound between strategy and operation on the one hand, and strategy and problem size on the other hand. To avoid these confounds, we designed a paradigm in which we manipulated presentation format, and stayed within one operation: subtraction. Furthermore, the arithmetic problems presented in these presentation formats were equal in problem size (all were subtractions below 10), bypassing this potential confound of problem size. This study is presented in ***Chapter 3***.

From this literature overview, we can conclude that the magnitude and verbal code also play a role in arithmetic in children. Additionally, deficits in exactly these codes have been observed in children with specific learning disorders (see Ashkenazi, Black, Abrams, Hoeft, & Menon, 2013 for a review).

1.3 The neural correlates of arithmetic in dyscalculia and dyslexia

Arithmetic constitutes one of children’s main subjects in primary school education, and properly acquiring this culturally designed, yet basic skill is of utmost importance during the first years of formal schooling. However, children with specific learning disorders often show deficits in arithmetic: children with dyscalculia are impaired on all aspects of arithmetic, and children with dyslexia often have difficulties retrieving arithmetic facts (see below). In the DSM-5 (American Psychiatric Association, 2013), learning disorders are classified under neurodevelopmental disorders, as they are presumed to be biological in origin. Nonetheless, and despite the relatively high prevalence of dyscalculia and dyslexia, the proportion of research dedicated to investigating their neurobiological origin is relatively low, especially compared to neurodevelopmental disorders similar in prevalence and severity, such as ADHD (Bishop, 2010). In the following sections, the limited neuroimaging research dedicated to arithmetic in dyscalculia and dyslexia is discussed.

1.3.1 Dyscalculia

Dyscalculia is characterized by persistent deficits in arithmetic, with scores of at least 1.5 standard deviations below the population mean for age. These deficits remain despite specifically targeted remediation and are not better accounted for by inadequate schooling or global developmental delays (e.g., visual, auditory or motor impairments, intellectual disability or other neurodevelopmental disorders) (American Psychiatric Association, 2013). *Behaviorally*, children with dyscalculia are impaired in arithmetic tasks. As reported above, previous research has reported a developmental shift during childhood from procedural strategy use towards an increased reliance on fact retrieval (Siegler, Adolph, & Lemaire, 1996; Siegler, 1996). Geary et al. (1987) found that children with dyscalculia have difficulties with this shift from procedural strategies towards retrieval. This leaves children with dyscalculia performing poorly on both procedural strategies and fact retrieval (see e.g., Geary et al., 2007).

At the *cognitive* level, a possible hypothesis regarding the deficit associated with dyscalculia is a domain-specific abnormality in processing numerical magnitudes (Ansari, 2008; Ashkenazi et al., 2013; Butterworth et al., 2011; Mazzocco, Feigenson, & Halberda, 2011; Rousselle & Noël, 2007; see De Smedt et al., 2013, for a review). However, others have put forward domain-general hypotheses as explanations for the arithmetic difficulties in dyscalculia, such as deficits in executive functioning including working memory (Rotzer et al., 2009; Toll, Van der Ven, Kroesbergen, & Van Luit, 2011) and attention (Askenazi & Henik, 2010). These two hypotheses are not mutually exclusive: it is not unlikely that both domain-specific and domain-general correlates could play a part in the deficits associated with dyscalculia.

Although dyscalculia is classified as a neurodevelopmental disorder, there is only a limited amount of neuroimaging research available in children dedicated to gaining more insight into the *neural* correlates of dyscalculia. Structural MRI research has shown reduced grey matter for children with dyscalculia in regions previously found to be associated with arithmetic in children: superior parietal lobule, intraparietal sulcus, fusiform gyrus and anterior temporal areas (Rykhlevskaia et al., 2009). DTI research has thus far also reported reduced white matter volume in children with dyscalculia in the temporoparietal cortex (Rykhlevskaia et al., 2009), and in left frontal and right parahippocampal areas (Rotzer et al., 2008). Ranpura et al. (2013) showed that, whereas white matter volume tends to increase with age in typically developing children, this increase was smaller or can even be reversed in children with dyscalculia. Furthermore, one functional connectivity study in children with dyscalculia showed hyper-connectivity of the intraparietal sulcus to frontal and other parietal regions, possibly indicating aberrations on a network level (Jolles et al., 2016). Similar findings of hyper-connectivity between the intraparietal sulcus and frontal and parietal areas were found using an effective connectivity analysis (Rosenberg-Lee et al., 2015).

Results from functional MRI research have thus far been mixed: both hypo-activation (with children with dyscalculia showing lower activity levels compared to typically developing children) and hyper-activation (higher activation for children with dyscalculia compared to typically developing children) have been reported. Berteletti, Prado and Booth (2014) used a region of interest approach, and delineated phonological areas such as the left inferior frontal gyrus and left temporal regions (i.e., verbal code) using a rhyming task, and numerical areas including the right superior parietal lobule (i.e., magnitude code) using a non-symbolic number comparison task. They reported hypo-activation in children with dyscalculia in both phonological and numerical areas during small (operands smaller or equal to 5) and large (operands larger than 5) multiplications. Ashkenazi, Rosenberg-Lee, Tenison and Menon (2012) also found hypo-activation in children with dyscalculia in posterior and inferior parietal regions and dorsolateral prefrontal cortex for small (one of the operands was always 1) and large (both operands below 10) additions using a whole brain approach. Kucian et al. (2006) found no differences in activation levels between children with dyscalculia and their typically developing peers for exact calculations, but reported hypo-activation in left intraparietal and inferior frontal regions in children with dyscalculia for approximate calculation. On the other hand, Rosenberg-Lee et al. (2015) found hyper-activation in children with dyscalculia on a whole brain level, more specifically in parietal, occipitotemporal and prefrontal regions, for single-digit addition and subtraction problems. Davis et al. (2009) also inspected brain activation on a whole brain level and reported hyper-activation in children with dyscalculia in parietal, frontal and cingulate cortices for exact and approximate calculations. Using a whole brain approach, De Smedt, Holloway and Ansari (2011) reported hyper-activation in the intraparietal sulcus for children with low levels of arithmetic ability during small additions and subtractions, but not during the solving of larger problems. This might indicate that children with low arithmetic ability continue to rely on procedural strategies (i.e., magnitude code) for smaller problems, whereas children with higher levels of arithmetic ability have already shifted towards retrieval, and are therefore showing lower activation levels in regions associated with procedural strategies (i.e., intraparietal sulcus).

Alternatively, it could also be the case that children with lower arithmetic ability recruit the magnitude code in an abnormal way during arithmetic.

Finally, it should be noted that previous fMRI studies have often used a lenient cut-off criterion for dyscalculia (e.g., children below the 25th percentile, see e.g., Ashkenazi et al., 2012). Caution is therefore required while interpreting these (rather inconsistent) results.

1.3.2 Dyslexia

Dyslexia is a much more intensively studied learning disorder compared to dyscalculia. Children with dyslexia show persistent deficits in reading abilities, with scores of at least 1.5 standard deviations below the population mean for age. These impairments remain despite specifically targeted interventions and are not better accounted for by inadequate schooling or global developmental delays (e.g., visual, auditory or motor impairments, intellectual disability or other neurodevelopmental disorders) (American Psychiatric Association, 2013). *Behaviorally*, dyslexia is characterized by problems with fluent reading.

At the *cognitive* level, these deficits are typically attributed to domain-specific deficits in phonological processing (Boada & Pennington, 2006; Elbro & Jensen, 2005; Ozernov-Palchik, Yu, Wang, & Gaab, 2016; Stanovich et al., 1994; Wagner & Torgesen, 1987), which can be defined as the ability to decode and manipulate phonemes in relation to their associated graphemes. However, also in dyslexia, the possibility of domain-general cognitive deficits, more specifically difficulties in working memory (Berninger, Raskind, Richards, Abbott, & Stock, 2008) and attentional processes (Shaywitz & Shaywitz, 2008, but see also the visual attention hypothesis, Facoetti, Turatto, Lorusso, & Mascetti, 2001) have been put forward. Again, these domain-specific and domain-general hypotheses do not exclude each other. Finally, deficits in procedural memory, associated with the automatization of cognitive skills, have been suggested in dyslexia (Nicolson, Fawcett, Brookes, & Needle, 2010), and, interestingly, more recently also in dyscalculia (Evans & Ullman, 2016).

At the *neural* level, research has shown that reading recruits a mostly left-lateralized whole brain network, with focus on the ventral occipitotemporal cortex for word recognition (the so called visual word form area; Baker et al., 2007), the left inferior frontal gyrus (Broca's area) for language comprehension, and the superior temporal gyrus for phonological decoding (see Houdé, Rossi, Lubin, & Joliot, 2010 and Martin, Schurz, Kronbichler, & Richlan, 2015 for meta-analyses). Structural MRI research has shown reduced grey matter volume in children with dyslexia compared to typically developing children in the left superior temporal sulcus and the right superior temporal gyrus (see Richlan, Kronbichler, & Wimmer, 2013 for a meta-analysis). Interestingly, anatomically similar superior temporal regions have been implicated in arithmetic and dyscalculia as well (see e.g., Rykhlevskaia et al., 2009). DTI studies have found reduced white matter volume in left temporoparietal and frontal areas in children with dyslexia, yet increased white matter in the corpus callosum, which interconnects both hemispheres (see Eden, Olulade, Evans, Krafnick, & Alkire, 2016; Gabrieli, 2009; Vandermosten, Boets, Wouters, & Ghesquière, 2012 for a review). This increase in connectivity between hemispheres could potentially reflect an increased reliance on right hemisphere compensatory processes in children with dyslexia. Meta-analyses and reviews of functional MRI research using reading-related tasks, such as phonological tasks (e.g., rhyming), have reported hypo-activation in the entire left-hemisphere reading network (ventral occipitotemporal cortex, inferior frontal gyrus and temporoparietal areas, see above), yet hyper-activation in the left precentral areas in children with dyslexia, again potentially pointing towards an increased reliance on compensatory mechanisms (see Eden, 2016; Gabrieli, 2009; Richlan, 2012 for reviews; see Richlan, Kronbichler, & Wimmer, 2009; Richlan et al., 2013 for meta-analyses).

Although deficits in arithmetic are not part of the criteria for a formal diagnosis of dyslexia, dyslexia is remarkably often accompanied by mild difficulties in arithmetic fact retrieval (De Smedt & Boets, 2010; Göbel, 2015; Simmons & Singleton, 2008; Träff & Passolunghi, 2015). Note that these arithmetic difficulties are often not severe enough to meet the diagnostic criteria of dyscalculia. A possible explanation for this finding is that arithmetic fact retrieval is influenced by phonological processes (De Smedt & Boets, 2010; De Smedt, Taylor, Archibald, & Ansari, 2010; Simmons & Singleton, 2008), which are compromised in people with dyslexia. Furthermore, Moll, Göbel and Snowling (2015) reported that children with dyslexia perform weaker compared to typically developing children on all tasks tapping into verbal number skills (counting, number identification, arithmetic and symbolic number comparison), which points towards weaker symbolic numerical magnitude processing skills in children with dyslexia. These weaker symbolic numerical magnitude processing skills might potentially also result into the fact retrieval deficits of children with dyslexia, although this remains uninvestigated to date.

Neurally, one region is jointly involved in arithmetic and reading: the left temporoparietal area. In arithmetic, this region is involved in retrieving arithmetic facts (see e.g., Grabner et al., 2009), in reading it is involved in phonological decoding (see Houdé et al., 2010 for a meta-analysis). However, this potential overlap of arithmetic and reading has not been thoroughly investigated in children with dyslexia. The only neuroimaging study thus far that has looked into the neural correlates of arithmetic in children with dyslexia is a study by Evans, Flowers, Napoliello, Olulade and Eden (2014). These authors found hypo-activation in children with dyslexia compared to typically developing children in left temporoparietal regions during the solution of small additions and subtractions. Additional analyses pointed out that, while typically developing children recruited this region differently for additions than for subtractions, children with dyslexia did not show this modulation in neural activation. This finding was explained by an atypical, and perhaps less efficient, approach to solving arithmetic problems in children with dyslexia compared to typically developing children.

Even though their arithmetic problems do not meet the diagnostic criteria for dyscalculia, children with dyslexia show impairments at the level of fact retrieval and potentially at the level of symbolic magnitude processing (see above). An intriguing question regarding the neural correlates of this retrieval deficit in children with dyslexia, is whether they are similar or dissimilar to the neural basis of arithmetic problems in children with dyscalculia. However, up to now, no research has directly compared children with dyslexia and children with dyscalculia in the context of arithmetic at the neural level, which we have investigated in ***Chapter 4***.

1.3.3 Comorbid dyslexia/dyscalculia

As mentioned above, the prevalence of the comorbidity between dyslexia and dyscalculia is remarkably high (around 40%; Wilson et al., 2015), yet vastly under-researched. In their narrative review, Ashkenazi et al. (2013) have suggested three possible pathways through which this comorbidity might occur. First, the comorbidity might come from an additive process, where the comorbidity between arithmetic and reading problems arises as a cumulative effect of both: a numerical magnitude processing deficit for dyscalculia (see e.g., Butterworth et al., 2011) and a phonological processing deficit for dyslexia (see e.g., Boada & Pennington, 2006). Second, the comorbidity might be verbally mediated. As described above, phonology and arithmetic, fact retrieval in particular, are closely related (De Smedt et al., 2010; Simmons & Singleton, 2008), and the role of phonological processing in reading has been well-established (Stanovich & Siegel, 1994; Wagner & Torgensen, 1987). Phonological deficits might therefore underlie deficits in both dyscalculia and dyslexia, and by extension in comorbid dyslexia/dyscalculia. Third, domain-general processes, not specific to dyslexia or dyscalculia, could be at the root of the comorbidity. In their meta-analysis, Houdé and colleagues (2010) described various shared, domain-general processes that are required for both arithmetic and reading, such as attention and working memory processes. Research by Haworth et al. (2009) has also shown high genetic correlations between reading and arithmetic ability, indicating a similar genetic influence that could potentially lie in domain-general processes. Finally, also multifactorial comorbidity models have been proposed (see e.g., Cramer, Waldorp, van der Maas, & Borsboom, 2010), suggesting that both domains-specific correlates (i.e., number and phonological processing deficits) and domain-general processes (e.g., working memory or attention) lie at the basis of the comorbidity.

Research on comorbid dyslexia/dyscalculia has so far solely been behavioral in nature. Landerl, Fussenegger, Moll and Willburger (2009) compared children with dyscalculia and children with dyslexia with children with comorbid dyslexia/dyscalculia, aged 8 to 10 years old. They reported additive effects: Children with comorbid dyslexia/dyscalculia showed deficits in phonological processing comparable to the deficits in children with dyslexia, and similar numerical magnitude processing deficits compared to children with dyscalculia. Likewise, Moll et al. (2015) also found an additive effect of comorbid dyslexia/dyscalculia, with comparable deficits for children with comorbid dyslexia/dyscalculia as in children with dyscalculia on numerical tasks, and impairments in verbal number tasks (i.e., counting, subitizing, calculation accuracy), equivalent to those in children with dyslexia. On the other hand, Willcutt et al. (2013) found that, next to domain-specific impairments in children with dyslexia and children with dyscalculia, children with dyslexia, dyscalculia and comorbid dyslexia/dyscalculia showed domain-general impairments as well, endorsing a multifactorial view on comorbidity that acknowledges the influence of both domain-general and domain-specific influences. Finally, Wilson et al. (2015) also reported both independent domain-specific and domain-general (i.e., verbal short-term memory) correlates of dyslexia and dyscalculia, be it in adults, supporting the multifactorial view.

Neuroimaging research dedicated to investigating the origin of the comorbidity between dyslexia and dyscalculia is currently non-existent. Even more, it has been vastly overlooked in previous research, as previous studies on dyslexia often did not take arithmetic ability into account, and studies on dyscalculia either did not take reading ability into account, or simply discarded participants with low reading ability. Therefore, in ***Chapter 4***, we looked into the neural correlates of this comorbidity by directly comparing the neural correlates of comorbid dyslexia/dyscalculia to the neural correlates of dyslexia-only and dyscalculia-only.

Finally, in ***Chapter 5***, we directly compared the domain-specific cognitive correlates associated with dyscalculia and dyslexia (i.e., numerical magnitude processing and phonological processing, respectively), and investigated the additive and under-additive hypotheses on the cognitive origin of comorbid dyslexia/dyscalculia.

1.4 fMRI and multivariate analyses

The majority of data in this doctoral dissertation was acquired using fMRI, which is a non-invasive method to visualize and measure task-related neural activity based on the proportion of oxygenated blood in the brain (Arthurs & Boniface, 2002). Using a general linear model, the effect of each experimental condition on the neural response is then estimated per individual voxel, and presented as a beta value (one per experimental condition).

Traditionally, fMRI data are analyzed using univariate analyses (see e.g., Berteletti et al., 2014; Evans et al., 2014; Prado et al., 2014; Rivera et al., 2005; Rosenberg-Lee et al., 2011). Two approaches can be followed: a region of interest (ROI) approach, or a whole brain approach. Using independent functional localizer scans, a specific ROI can be accurately delineated per subject. The beta values per experimental condition of all the voxels of that ROI are subsequently averaged. The mean beta values in that specific ROI per condition can then be statistically compared (see Figure 1.2 A). On the other hand, using a whole brain approach, it is possible to look for statistical differences between conditions per voxel over the entire brain. In all neuroimaging studies included in this doctoral dissertation, either ROI-based (***Chapter 2***), or whole brain univariate analyses (***Chapters 3 and 4***) were performed.

Univariate analyses are associated with the drawback that differences between conditions or between groups of participants run the risk of being averaged out, and thus overlooked (Norman, Polyn, Detre, & Haxby, 2006). However, by taking the spatial pattern of activation into account using a multi-voxel pattern analysis (MVPA) approach, and thereby looking at the contributions of multiple voxels simultaneously, more subtle, finer scaled differences between conditions or subject groups can be picked up (see Norman et al., 2006). Furthermore, it is also possible to look into the neural (dis)similarity of conditions and subject groups. In this doctoral dissertation, three types of MVPA were used: correlational analyses, subject classification analyses, and subject generalization analyses.

In ***Chapter 2***, a multivariate correlational analysis was performed (see Figure 1.2 B, and see Boets et al., 2013 for a similar approach). In this analysis, the acquired functional data were divided into two halves for all subjects. Subsequently, the neural activation patterns of all conditions of the first half of the data were correlated with the neural activation patterns of the conditions of the second half in predefined ROIs. This cycle of dividing data into halves and correlating the activation patterns of the first with the second half of data was repeated 100 times, then averaged per subject, and finally averaged over all subjects. The obtained correlational matrices then indicated per ROI which conditions were more correlated and hence more similar in terms of the elicited neural activation patterns. This way, a multivariate correlational analysis provides an indication of the neural similarity of experimental conditions in a predefined ROI.

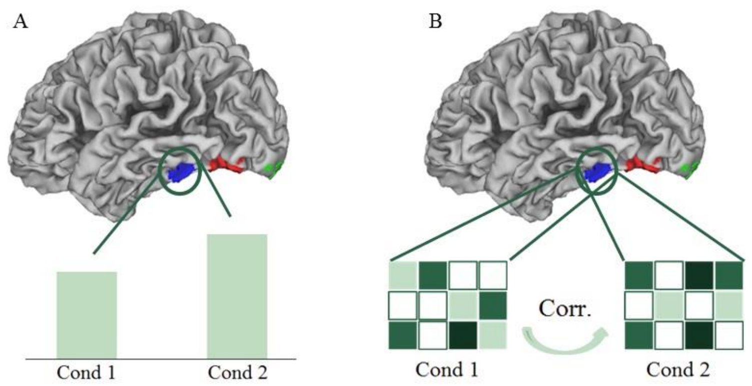

Figure 1.2. Schematic presentation of a univariate (A) and multivariate correlational analysis (B).

In ***Chapter 4***, both multivariate subject classification and subject generalization analyses were used. In the subject classification analysis (see Figure 1.3), a model was trained to classify subjects from two distinct groups solely based on their neural activation patterns elicited by a specific condition in a specific ROI. A subset of participants from both groups was used to *train* a model to learn to distinguish between the two groups based on the neural activation patterns elicited by the different conditions. Subsequently, the model was *tested* by providing it solely with the neural activation patterns of the remaining subjects, and by subsequently estimating the accuracy with which the model could correctly classify subjects as belonging to their group. This analysis allowed us to investigate whether the neural activation patterns elicited in different groups of subjects were distinct or rather similar.

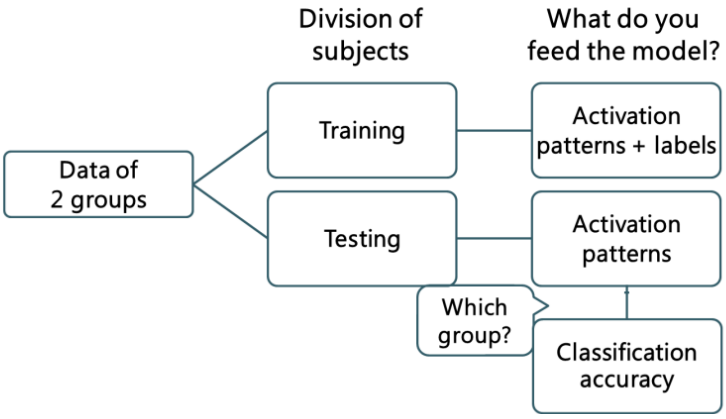

Figure 1.3 Schematic overview of subject classification analysis.

Using a subject generalization analysis (see Figure 1.4), the similarity or dissimilarity of subject groups in terms of neural activation patterns elicited by a specific condition in a specific ROI was inspected. In this analysis, the model was *trained* on distinguishing between two subject groups (i.e., groups 1 and 2) based on the neural activation patterns of the subjects (cfr. subject classification analysis). However, the model was subsequently *tested* on distinguishing between groups 1 and 3. The generalization accuracy then indicated how accurate the model was in classifying subjects from group 1 as belonging to group 1, and subjects from group 3 as belonging to group 2 (as the model had trained on distinguishing groups 1 and 2). In other words, this generalization accuracy is only significant, if the neural activation patterns from subjects from groups 2 and 3 were interchangeable, and hence very similar.

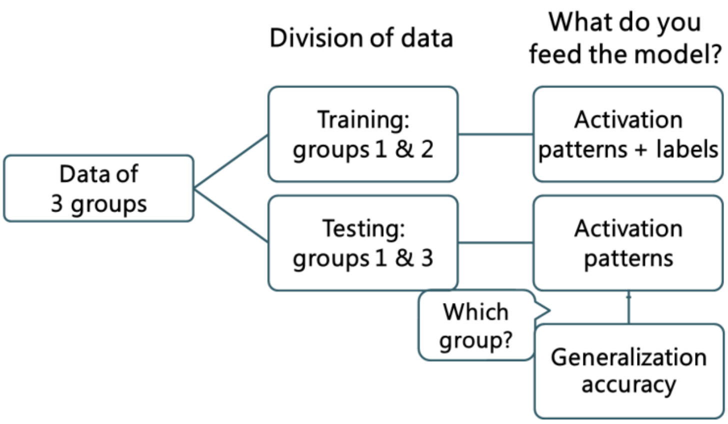

Figure 1.4. Schematic overview of subject generalization analysis.

1.5 Aims of the doctoral project

Throughout this doctoral dissertation, we attempted to supplement detected gaps in the literature on the neural correlates of arithmetic using three fMRI studies and a behavioral study.

First, the neural correlates of the visual code have been under-investigated so far, although most of the time we calculate using Arabic digits, and the visual code is particularly important for processing these Arabic number forms. Furthermore, the involvement of the ventral occipitotemporal cortex, assumed to host the visual code, has been repeatedly reported in the context of arithmetic (see Menon, 2015 for a review). Nonetheless, the exact role and anatomical location of this visual code remains unclear to date. In ***Chapter 2***, we therefore investigated the distribution of the visual processing of number forms in occipital and occipitotemporal cortex in the context of arithmetic. Furthermore, we studied how this processing of Arabic digits (visual code) emerges throughout the ventral visual processing stream using a multivariate correlational analysis.

Second, most neuroimaging research on arithmetic is based on the Triple Code Model, which is an adult-based model that is not necessarily generalizable to children. It is not clear whether the processes described to be involved in arithmetic in adults are comparable and have similar neural correlates in children, let alone if they are similarly involved in arithmetic. In ***Chapter 3***, the neural processes during arithmetic, more specifically during subtraction in different formats, were investigated in typically developing children.

Third, previous research in children with learning disorders has pointed towards deficits in numerical magnitude processing (magnitude code) and deficits in phonological processing (linked to the verbal code) underlying dyscalculia and dyslexia, respectively. Furthermore, arithmetic difficulties have not only been described in dyscalculia and comorbid dyslexia/dyscalculia, but also in dyslexia. However, the neurobiological correlates of arithmetic in dyscalculia, dyslexia, and comorbid dyslexia/dyscalculia remain unclear to date, as well as the generality or specificity of the neurobiological origin of these disorders. Therefore, in ***Chapter 4***, children with dyscalculia, dyslexia and comorbid dyslexia/dyscalculia were directly compared to each other and to age-matched typically developing children at a neural level during a subtraction task in different formats. Given the arithmetic nature of the task, we expected children with dyscalculia and children with comorbid dyslexia/dyscalculia to perform poorly on the symbolic formats (Arabic digits and number words) as well as on the non-symbolic format (dot arrays). On the other hand, as children with dyslexia have been found to show difficulties with verbal, symbolic aspects of arithmetic (see e.g., Moll et al., 2015), we expected them to perform poorly on symbolic formats only.

Fourth, only few behavioral studies to date have directly compared the cognitive correlates influencing dyscalculia and dyslexia. Moreover, a number of potential hypotheses describing the cognitive origin of comorbid dyslexia/dyscalculia have been proposed (see e.g., Ashkenazi et al., 2013), yet studies have not always led to similar conclusions. In ***Chapter 5***, we investigated the domain-specific cognitive correlates assumed to influence dyscalculia and dyslexia, to add to this literature.

As described above, we used both univariate and multivariate analyses to analyze the functional imaging data collected. These analyses allowed us to look into neural activation on a fine-grained scale, providing us with a detailed insight into the neural correlates of arithmetic in adults and children with and without learning disorders.

CHAPTER 2

The neural representation of Arabic digits in visual cortex

Published as

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Abstract

In this study, we investigated how Arabic digits are represented in the visual cortex, and how their representation changes throughout the ventral visual processing stream, compared to the representation of letters. We probed these questions with two fMRI experiments. In Experiment 1, we explored whether we could find brain regions that were more activated for digits than for number words in a subtraction task. One such region was detected in lateral occipital cortex. However, the activity in this region might have been confounded by string length – number words contain more characters than digits. We therefore conducted a second experiment in which string length was systematically controlled. Experiment 2 revealed that the findings of the first experiment were task dependent (as it was only observed in a task in which numerosity was relevant) or stimulus dependent (as it was only observed when the number of characters of a stimulus was not controlled).

We further explored the characteristics of the activation patterns for digit and letter strings across the ventral visual processing stream through multi-voxel pattern analyses. We found an alteration in representations throughout the ventral processing stream from clustering based on amount of visual information in primary visual cortex towards clustering based on symbolic stimulus category higher in the visual hierarchy. The present findings converge to the conclusion that in the ventral visual system, as far as can be detected with fMRI, the distinction between Arabic digits and letter strings is represented in terms of distributed patterns rather than separate regions.

2.1 Introduction

The vast majority of research on how numbers are processed in the brain has focused on the semantic representation of numbers, i.e., the magnitude a number represents. However, little is known about the visual processing of numbers, even though this type of processing has been claimed to be important when doing arithmetic (Dehaene & Cohen, 1995, 1997; Menon, 2015). We focused on the ventral visual processing stream, because this pathway plays a role in the identification and categorization of visual objects, such as digits. We investigated which regions in the visual cortex were activated whilst participants calculated with numbers in symbolic (e.g., Arabic digits and number words) and non-symbolic (dot arrays) formats.

The most commonly used theoretical framework to study number processing and arithmetic is the Triple Code Model (Dehaene & Cohen, 1995, 1997). According to this model, three distinct codes of numerical information can be activated. First, the *visual* code is involved in processing Arabic number forms, and in recognizing and discriminating number-letter strings. This process is assumed to take place in the inferior ventral occipitotemporal areas. Second, there is an analogue quantity or *magnitude* code which represents, estimates and compares numerosities (Ansari, 2008; Nieder & Dehaene, 2009), and is implicated when we manipulate numerosities, as during arithmetic (Bulthé, De Smedt, & Op de Beeck, 2014; Dehaene et al., 2003; Eger et al., 2009; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002). This code is located in the inferior parietal areas, and more specifically in the intraparietal sulci. Third, there is a *verbal* code in which numbers are represented by words. This code is located in the left-hemispheric perisylvian areas and in the left angular gyrus (Dehaene et al., 2003) and is implicated in accessing memory of arithmetic facts (Delazer et al., 2003; Grabner et al., 2009). A recent meta-analysis by Arsalidou & Taylor (2011) confirmed these regions as being involved in arithmetic, but they suggested to update this model by including regions such as frontal areas, cerebellum, insula and cingulate cortex.

Although the roles of the magnitude and verbal codes have been extensively studied, the *visual* code has not been studied much in the context of arithmetic (Menon et al., 2014). In their description of the Triple Code Model, Dehaene and Cohen (1995, 1997) suggested that this code should be located in occipitotemporal regions, along the visual ventral processing stream, which plays a role in identification and categorization of objects (Goodale & Milner, 1992; Mishkin, Ungerleider, & Macko, 1983). There is a large body of studies that directly investigated the coding of objects (Grill-Spector, Kourtzi, & Kanwisher, 2001; Reddy & Kanwisher, 2006), faces (Halgren et al., 1999; Rossion et al., 2003), and even words (Baker et al., 2007; Cohen & Dehaene, 2004) in this ventral visual pathway (see also Grill-Spector & Malach, 2004; Malach, Levy, & Hasson, 2002). However, similar data on the coding of numerical symbols, such as Arabic digits, have not been reported. Dehaene and Cohen (1995) stated that, similar to a visual region specifically tuned for letter strings (visual word form area, VWFA), there should also be region specifically tuned for digits, hosting the visual code. Furthermore, studies have shown that occipitotemporal regions are activated together with the IPS during arithmetic (Keller & Menon, 2009; Rickard et al., 2000; Rosenberg-Lee, Chang, Young, Wu, & Menon, 2011; Wu et al., 2009; Zago et al., 2001), invigorating Dehaene and Cohen's claim that also visual regions in the occipitotemporal areas are involved in arithmetic. This hypothesis is further backed by results from a recent meta-analysis of studies using number processing or arithmetic tasks in healthy adult samples. Specifically, Arsalidou & Taylor (2011) found that the left fusiform gyrus is involved in number processing and arithmetic tasks, and that the left inferior occipital gyrus is implicated in subtraction tasks.

Only a small number of studies specifically attempted to find a brain region that could host this visual number processing code, a so-called *visual number form area* (Dehaene & Cohen, 1995; Menon, 2015), yet their findings are mixed. For example, Park, Hebrank, Polk, & Park (2012) found a cluster of voxels in the right lateral occipital area that was activated more by number strings than by letter strings in the context of a visual matching task, during which participants were presented with either two letter strings or two digit strings, and had to decide whether the two strings were visually identical. Polk et al. (2002) conducted a study with a similar paradigm, in which participants passively viewed strings of consonants, strings of digits, strings of shapes and fixation points. They did not find a region that was more activated by digits than by letters. However, in a subset of individuals, they found various regions in the visual cortex, especially around the left fusiform gyrus and left inferior regions, which were more active when viewing digits than fixation points. Pinel, Dehaene, Rivière, & Le Bihan (2001) observed a region in the right fusiform gyrus that was activated more when participants performed a number comparison task (i.e., deciding whether a number was larger or smaller than 65) with digits compared to with number words. Finally, using intracranial electrophysiological recordings, Shum et al. (2013) found a region in the inferior temporal gyrus that responded more to digits compared to morphologically, phonologically and semantically similar symbols.

The studies described above all focus on the role of the occipitotemporal cortex in number processing. However, although this brain area is also implicated in arithmetic (see above), previous studies with arithmetic tasks merely reported activity in the occipitotemporal cortex, but crucially, they did not look into the visual cortex specifically in the context of arithmetic (Keller & Menon, 2009; Pinel & Dehaene, 2013; Rickard et al., 2000; Wu et al., 2009; Zago et al., 2001) and thus did not clarify the role the visual cortex plays in arithmetic.

The current study serves two aims. First of all, we will investigate to what extent there is a focal region in the ventral visual system specifically tuned for Arabic digits that might host the visual code. Unlike previous studies, we will use an arithmetic paradigm with different formats to present numerosities for two reasons. First, activation in regions in the occipitotemporal cortex, where the visual code is thought to be located, has been found to be associated with arithmetic (see above). Second, including multiple formats (i.e., dot arrays, Arabic digits and number words) will allow us to isolate the visual code better by contrasting arithmetic with Arabic digits from arithmetic with number words. Both conditions include a symbolic format, and they mainly differ in the degree to which they are supposed to activate the visual code in the Triple Code Model.
Second of all, we will study the emergence and formation of this visual code by looking at the evolution of how digits are represented throughout the ventral visual processing stream. In order to do so, we will delineate three key regions along this ventral visual processing stream: primary visual cortex, lateral occipital complex and visual word form area. We selected these regions because of their specific characteristics: primary visual cortex is the first visual processing region, lateral occipital complex is specifically tuned to visual objects (Grill-Spector et al., 2001), and finally, visual word form area responds highly to visually presented letter strings (Baker et al., 2007). Using multi-voxel pattern analysis, we will compare activation patterns of all conditions to investigate the similarity with which conditions are represented in those regions of interest, and how these similarities change throughout the ventral visual processing stream. A great advantage of multivariate analyses is that they can reveal differences between conditions that are possibly averaged out in univariate analyses (Norman, Polyn, Detre, & Haxby, 2006; Raizada & Kriegeskorte, 2013).

2.2 Materials and Methods

2.2.1 Participants

Twelve healthy Dutch-speaking university students and employees took part in this study (four males, aged between 18 and 38 years old, *M* = 24.7, all right-handed), which consisted of two fMRI experiments. All participants had normal or correct-to-normal vision, and reported no history of neurological or psychiatric illness. Participants gave written consent prior to taking part in the study, and were paid for their participation. The study was approved by the Medical Ethical Committee of KU Leuven.

2.2.2 Apparatus

Imaging data were collected via a 3T Philips Intera Scanner, located at the Department of Radiology of the University Hospital in Leuven, with a 12-channel head coil. Functional images were collected with an EPI sequence (47 slices, 2 x 2 mm in plane voxel size, slice thickness 2 mm, interslice gap 1 mm, TR = 3000 ms, TE = 30 ms, flip angle = 90 degrees, 104 x 104 matrix). We acquired a high-resolution T1-weighted anatomical image (182 slices, resolution 0.98 × 0.98 × 1.2 mm, TR = 9.6 ms, TE = 4.6 ms, 256 × 256 acquisition matrix) for each participant. Stimuli were presented with PsychToolbox 3 (Brainard, 1997) and displayed via a Barco 6400i LCD projector onto a screen located approximately 35 cm from participants' eyes, which was visible via a mirror attached to the head coil. Participants answered by pressing one of two response buttons on a response box, which they controlled with their right hand.

2.2.3 Experimental tasks

2.2.3.1 Experiment 1

In the first experiment, participants performed a subtraction task in which they were asked to subtract two magnitudes (up to 20), and to decide whether the result was larger or smaller than a reference magnitude. We manipulated presentation format (dot arrays, Arabic digits or number words) and reference magnitude (4, 8 or 12). We investigated the effect of presentation format on behavioral results and on brain activation; reference magnitude was manipulated merely to insure sufficient variation in the numerosities used in the task and was not included in analyses.

One experimental run consisted of 4 fixation blocks of 15 seconds, alternated with 3 long reference blocks in which the participant had to compare the result of a subtraction to a specific reference magnitude (4, 8 or 12). Each reference block consisted of 6 format blocks (2 blocks per presentation format) of 16.1 seconds each. Each of these format blocks consisted of a presentation of the specific reference magnitude in the specific format, and 6 items in that format. Half of the subtraction items were smaller than the given reference, half of them larger. In total, a run lasted 349.8 seconds, and participants performed 6 runs. The design is further illustrated in Figure 2.1.

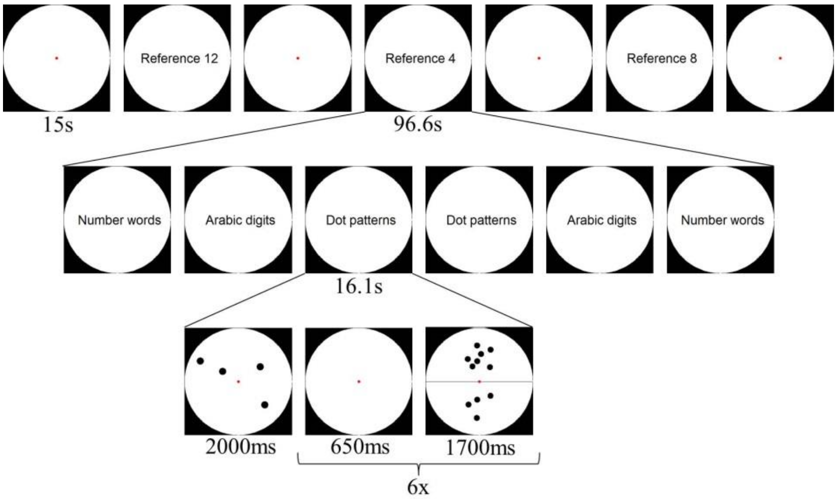

Figure 2.1. Schematic overview of a possible design of an experimental run of Experiment 1.

Stimuli were presented in a white circle on a black background divided into two halves by a horizontal black line. The numerosity presented in the lower half of the circle had to be subtracted from the numerosity in the upper half (see Figure 2.2). Items presented as dot arrays were created via a Matlab script (Dehaene, Izard, & Piazza, 2005) and were controlled for parameters such as item size, total area and luminance by manipulating dot size. Furthermore, items presented as Arabic digits and number words were controlled for amount of visual information, by varying the font size and position within the circle (see Figure 2.2). As all participants were Dutch speaking, number words were presented in Dutch. These stimuli were created using an adapted version of the Matlab script by Dehaene, Izard, & Piazza (2005).

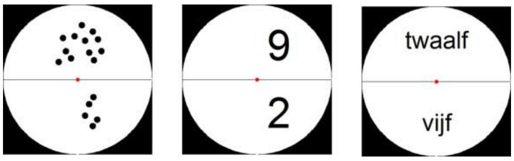

Figure 2.2 Examples of stimuli from Experiment 1: stimuli presented as dot arrays, Arabic digits and (Dutch) number words.

2.2.3.2 Experiment 2

Although we controlled the stimuli from Experiment 1 for the amount of visual information (i.e., number of black pixels in the stimulus), it is evident that number words always consist of more visual elements (i.e., multiple letters) than digits (i.e., one or two elements). Previous research has shown that visual regions, such as the lateral occipital complex (LOC), can be sensitive to the number of visual elements presented (Xu & Chun, 2006; Xu, 2008). To control for this potential confound of the number of visual elements on the screen, participants performed a second fMRI experiment immediately after Experiment 1. In Experiment 2, both string length (2 or 5 characters) and character format (Arabic digits or letters) were manipulated. Participants performed an order judgment task: They were asked to indicate whether the ordering of the first character relative to the last character was correct or not. In the two digit conditions (both 2 and 5 characters), the ordering was correct if the first character was numerically smaller than the last character. In the letter conditions, alphabetical order was correct. Four blocks per condition alternated with five fixation blocks were presented during this experiment, with each block lasting 12 seconds. Within each trial block, 6 stimuli were presented. Total duration of one run was 252 seconds, and participants performed 4 runs. The design of Experiment 2 is illustrated in Figure 2.3.

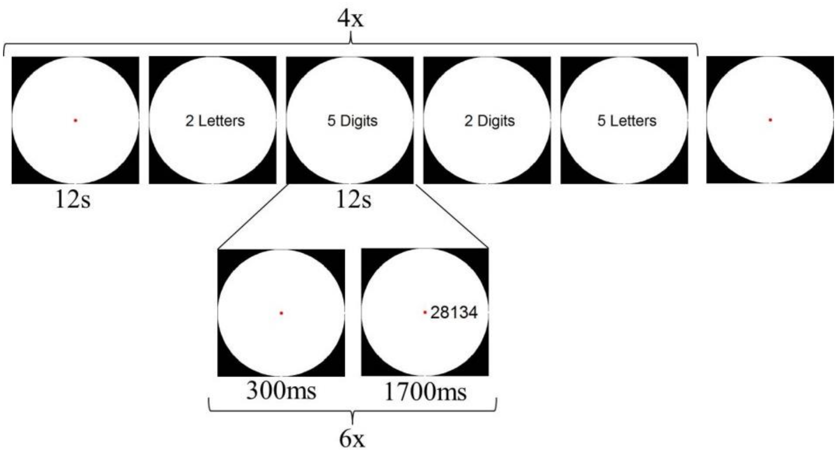

Figure 2.3. Schematic overview of a possible design of Experiment 2.

Stimuli were presented in a white circle on a black background. For digit conditions, Arabic digits 1 to 9 were used in the creation of the random digit strings. In the letter conditions, 9 letters, which were visually similar to the digits, were selected: a, c, e, n, r, s, v, x, and z. None of the letter strings represented existing words. The stimuli were again created by adapting the Matlab script by Dehaene, Izard, & Piazza (2005). We controlled for visual parameters by varying font size and placement within the circle (see Figure 2.4).

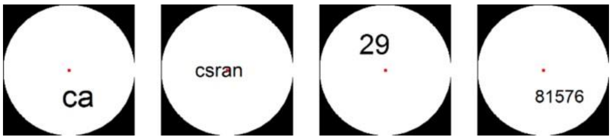

Figure 2.4. Examples of stimuli from Experiment 2: 2- and 5-character letter and digit strings.

<u>*2.2.4 Analyses*</u>

2.2.4.1 Behavioral analyses

The behavioral data from both experiments were analyzed with SPSS (IBM SPSS Statistics 22; IBM Corp., Chicago, IL, USA). We controlled for multiple comparisons via a Bonferroni correction. This was done by multiplying each specific *p*-value by the number of contrasts calculated in that analysis. The alpha-criterion therefore remained .05.

2.2.4.2 fMRI preprocessing

All imaging data were preprocessed using the Statistical Parametric Mapping software package (SPM8, Wellcome Department of Cognitive Neurology, London). Functional images were corrected for slice-timing differences, as well as head motion artifacts by realigning all images to the first image. All functional images were coregistered to the anatomical image. Both functional and anatomical images were normalized to the standard Montreal Neurological 152-brain average template. Finally all functional images were spatially smoothed using a Gaussian kernel of 4 mm full-width at half maximum (FWHM). The effect of experimental conditions per voxel was estimated by creating a general linear model per participant. The fixation condition was not explicitly modeled. Motion realignment parameters were included as regressors to control for variation due to movement artifacts.

2.2.4.3 Regions of interest

To identify different stages of visual processing in each participant, we ran a separate localizer task to localize three visual processing regions of interest: primary visual cortex (V1), lateral occipital complex (LOC) and visual word form area (VWFA). During the localizer runs, words, line drawings of objects, and scrambled lines were presented for 300 ms in a block design. Participants were asked to respond to a word or object if it represented a living entity, and to a scrambled pattern if it was oriented vertically. V1 was localized by selecting all voxels in Brodmann area 17 (located with the anatomical WFU PickAtlas Toolbox, Wake Forrest University PickAtlas, http://fmri.wfubmc.edu/cms/software) that were significantly active in all stimulus conditions versus fixation. LOC was defined by the contrast [objects – scrambled lines]. Finally, we delineated VWFA by the contrast [words – objects]. The statistical threshold for the ROI selection was $p < .001$, uncorrected for multiple comparisons.

2.2.4.4 fMRI analyses

Both univariate and multivariate correlational analyses were performed on the beta values of the individual conditions as obtained from the general linear model of both fMRI experiments. All functional data were smoothed before the general linear model was estimated (see section 2.2.4.2), as spatial smoothing is a standard practice for univariate analyses, and is also beneficial for the effect size in correlational multivariate analyses (Brants, Baeck, Wagemans, & Op de Beeck, 2011; Op de Beeck, 2010).

In univariate analyses, we averaged the brain activation per condition over all the voxels in a certain region of interest, and compared these mean activations (beta values) over conditions (see Figure 2.5A). In the multi-voxel correlational analyses, we divided the dataset into two halves, and correlated the patterns of activation of all conditions of the first half of the data with the second half, in the delineated regions of interest. This cycle of dividing data and correlating patterns was repeated 100 times; the correlations reported below are the average correlations over those repetitions, which were then transformed via a Fisher-z transformation, and were finally averaged over all subjects. In the multi-voxel patterns, the activation of each voxel for each condition was expressed in terms of the beta value of that condition subtracted by the mean beta value across all experimental conditions ("cocktail blank normalization"). Because of the normalization, positive correlations between their activity patterns in a certain brain region indicate more similarity between the corresponding conditions (see Figure 2.5B). The main advantage of multivariate analyses is that they can reveal differences between conditions that are possibly averaged out in univariate analyses (Norman et al., 2006). To visualize the results obtained from the multivariate correlational analyses, we performed multidimensional scaling (MDS) on the obtained averaged correlation matrices. MDS visualizes the similarity of conditions in 2D-space, with conditions that are represented similarly, and hence have higher correlated activation patterns, presented closer together. Conditions that are represented more distinctly (lower correlated activation patterns) will be shown further apart in the MDS visualization. We also determined the coordinates of the conditions in the MDS plots for each individual subject. These coordinates were then rotated using a Procrustes analysis, to fit the space of the MDS plots of the average correlation matrix. The rotated coordinates of each subject will be used as error bars in the MDS plots.

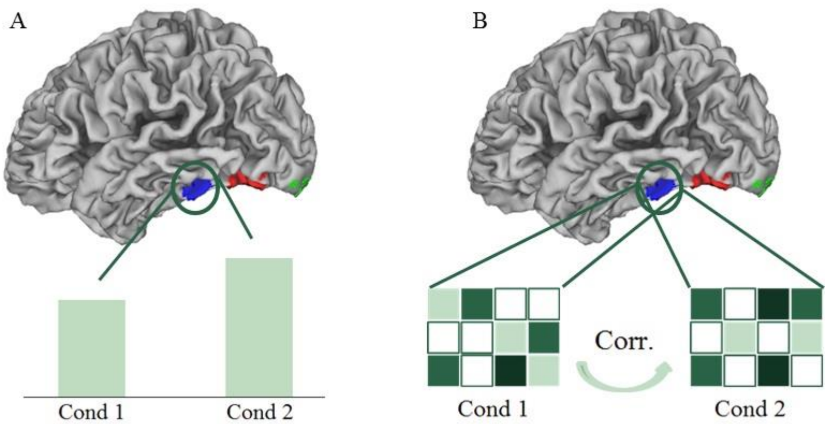

Figure 2.5. Schematic presentation of a univariate (A) and multi-variate correlational analysis (B). In univariate analyses, we averaged the brain activation per condition over all the voxels in a certain region of interest. In multi-voxel correlational analyses, we correlated the patterns of activation of all conditions.

2.3 Results

<u>*2.3.1 Experiment 1*</u>

2.3.1.1 Behavioral results

Mean accuracy and reaction time were calculated over runs and participants (see Table 2.1). A one-way repeated measures ANOVA with format (dots vs. digits vs. words) as within-subject factor was performed on both the accuracies and the reaction times. Regarding the accuracy scores, we found a main effect of format ($F_{(2,22)} = 70.79$, $p < .001$). Pairwise contrasts showed that the accuracy for dot arrays was lower than that for Arabic digits and number words (both p's < .001). Accuracy for Arabic digits was significantly higher than that of number words ($p = .01$). Turning to the response latencies, we again found a significant main effect of format ($F_{(2,22)} = 12.65$, $p < .001$). Participants were significantly faster in responding to dot arrays and Arabic digits than to number words ($p = .03$ and $p < .001$, respectively). The difference in reaction time between dot arrays and Arabic digits was not significant ($p = .84$).

Table 2.1

Behavioral results Experiment 1

	RT (ms)	*SD*	% Correct	*SD*
Dot arrays	1151	146	69.56	9.55
Arabic digits	1108	191	87.58	9.94
Number words	1260	183	82.41	13.29

2.3.1.2 Imaging results

First, we used a whole-brain analysis to determine which regions might be hosting the visual code. Analogous to previous studies (e.g., Pinel, Dehaene, Rivière, & LeBihan, 2001), this was done by comparing the brain activity of Arabic digits vs. words. Both conditions included a symbolic format with which participants had to calculate, and they mainly differed in the degree to which they were supposed to activate the visual code in the Triple Code Model. There was only one brain region showing higher activity for Arabic digits than for number words, namely the bilateral lateral occipital cortex (see Figure 2.6).

The opposite contrast (number words > Arabic digits) showed activation in the occipital lobe around primary visual cortex, which is probably related to the fact that the number words comprise more characters, and thus extend more to the left and the right with respect to the fixation point than digits.

Figure 2.6. Bilateral lateral occipital activation clusters from contrast [digits – words] in Experiment 1. MNI coordinates of peak voxels are [49 -71 9] and [-44 -67 14].

Next, we analyzed the data in our three visual regions of interest, i.e., V1, LOC and VWFA. (see Figures 2.7 and 2.8). In V1, dot arrays and number words elicited more activation than Arabic digits did (both p's < .001), whereas dot arrays and number words did not differ in terms of activation (p = .07). The same pattern was found, though with smaller effect size, in LOC: dot arrays and number words activated this region more than Arabic digits did (p = .003 and p = .01, respectively), whereas dot arrays and number words did not differ in terms of activation (p = .91). Furthermore, this analysis revealed that the lateral occipital region specifically activated by Arabic symbols was not overlapping with our functionally defined LOC. Finally, in the third a priori defined region of interest, the visual word form area (VWFA), we found significantly more activation for number words than for digits (p < .001), and higher activation for digits than for dot arrays (p = .005).

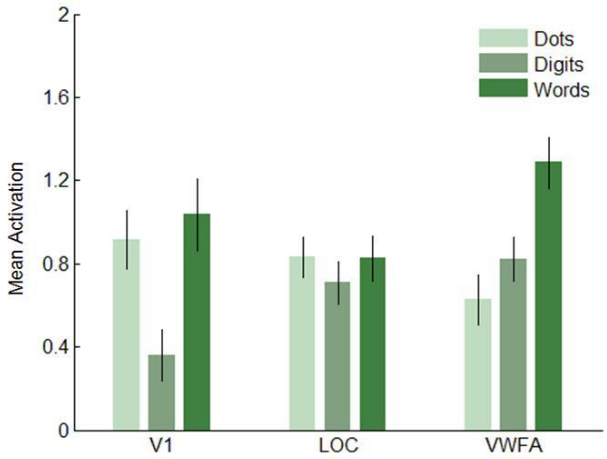

Figure 2.7. Mean activation elicited by the three format conditions in the three regions of interest in Experiment 1. Error bars represent standard error of the mean.

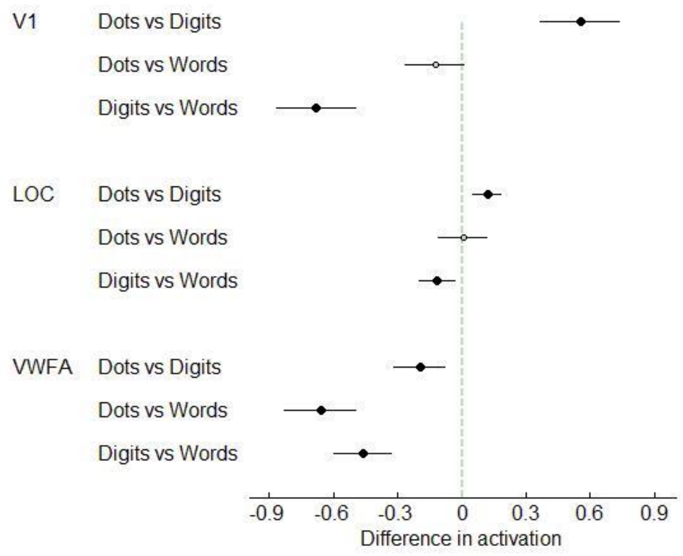

Figure 2.8. T-values of the contrasts between conditions in Experiment 1. Error bars represent a 95% confidence interval. Significant t-tests are represented by black, larger dots. T-tests that did not reach significance, are represented as open, smaller dots.

2.3.2 Experiment 2

2.3.2.1 Behavioral results

Mean reaction time as well as mean accuracy were calculated for each participant and averaged over runs (see Table 2.2). A two-way repeated measures ANOVA with format (letters vs. digits) and string length (2 vs. 5) as within-subject factors was performed both on the reaction time and the accuracy scores. We found a significant main effect of format ($F_{(1,11)} = 159.32$, $p < .001$) and of string length ($F_{(1,11)} = 88.42$, $p < .001$) for the reaction time data. Digit strings were solved faster than letter strings, and 2-character strings were solved faster than 5-character strings. Also, the interaction effect between format and string length was significant ($F_{(1,11)} = 26.78$, $p < .001$). This effect was driven by a smaller difference between the two letter conditions compared to the two digit conditions. Regarding the accuracy scores, only a main effect of format was found ($F_{(1,11)} = 26.10$, $p < .001$), indicating that digit strings were solved more accurately than letter strings. The effect of string length and the interaction effect were not significant ($F_{(1,11)} = .87$, $p = .37$ and $F_{(1,11)} = 1.13$, $p = .31$, respectively).

Table 2.2

Behavioral results Experiment 2

	RT (ms)	*SD*	% Correct	*SD*
2 Letters	956	147	90.02	7.72
5 Letters	996	151	90.03	8.72
2 Digits	792	148	98.26	3.31
5 Digits	885	162	97.05	3.93

2.3.2.2 Imaging results

In this second experiment, we investigated brain activity in response to our four conditions in five regions of interest: V1, LOC, VWFA and the two [digits – words] clusters found in Experiment 1. These results are presented in Figure 2.9 (univariate) and in Table 2.3 and Figure 2.11 (multivariate).

We first performed a two-way ANOVA with format (letters and digits) and string length (2 and 5 characters) as within-subject factors in every region of interest. In V1, we found a significant main effect for string length, with higher activity levels for 5-character than for 2-character strings ($F_{(1,11)} = 23.72$, $p < .001$), as well as a significant main effect of format ($F_{(1,11)} = 5.50$, $p = .04$), indicating that letters elicited more activation in V1 than digits. In LOC, only the effect of format was significant ($F_{(1,11)} = 64.72$, $p < .001$). Again, letters elicited more activation than digits. In VWFA, we found a significant main effect of format ($F_{(1,11)} = 126.70$, $p < .001$) and of string length ($F_{(1,11)} = 5.44$, $p = .04$), with letters and 5-character strings eliciting more activation, respectively. In the left [digits – words] region, the effect of format was significant ($F_{(1,11)} = 6.38$, $p = .03$), with letters eliciting higher activation levels, and in the right [digits – words] region, the effect of format, the effect of string length and the interaction effect were significant ($F_{(1,11)} = 9.46$, $p = .01$; $F_{(1,11)} = 9.29$, $p = .01$; $F_{(1,11)} = 5.52$, $p = .04$, respectively).

We also performed a three-way ANOVA with format (letters vs. digits), string length (2 vs. 5 characters) and region of interest (V1 vs. VWFA) as within subject factors. We found a significant three-way interaction ($F_{(1,11)} = 7.03$, $p = .02$). This interaction reflects that in VWFA, the activation increase for letters vs. digits was similar for 5- and 2- character sequences, while in V1 the activation increase for letters vs. digits was stronger for 2-character strings compared to 5-character strings (see Figure 2.10).

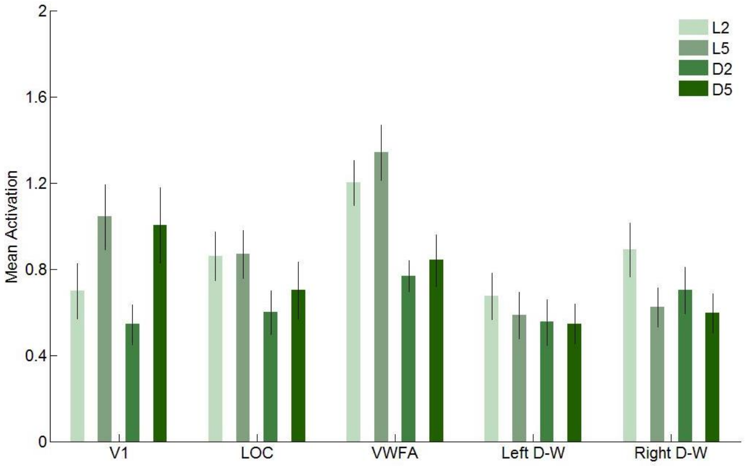

Figure 2.9. Mean activation elicited by the four conditions in the five regions of interest in Experiment 2. Error bars represent standard error of the mean.

We did not find a significant main effect of format in favor of digits in the [digits – words] regions found in Experiment 1. Thus, the preference for digits over words from Experiment 1 was not replicated in Experiment 2. This indicates that the area observed in Experiment 1 is not specifically sensitive to Arabic digits. In other words, the current data did not confirm the existence of a visual number form area.

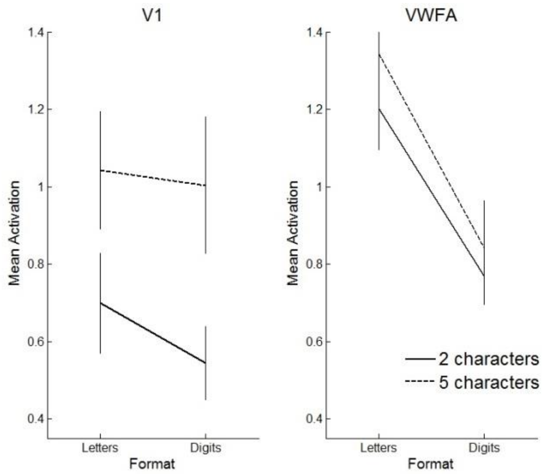

Figure 2.10. Visualization of the three-way interaction effect. Solid lines represent 2-character strings, dashed lines 5-character strings. In V1, the effect of string length is clearly more pronounced than the effect of format, whereas in VWFA, the opposite pattern is visible. Error bars represent the standard error of the mean.

Turning to multi-voxel analyses, we found a transformation in the representation of the four conditions across the regions of interest. In all regions of interest, we compared correlations between conditions that only differed in one factor (i.e., same format strings differing in length to look into the effect of string length) with correlations between the condition and itself (located on the diagonal of the correlational matrix, see Table 2.3). In V1, we found a significant effect of string length ($t(11) = -4.83$, $p = .001$), which indicates that activation patterns in V1 are sensitive to the number of characters on the screen. The effect of format was not significant ($t(11) = -0.91$, $p = .38$), indicating that V1 is not sensitive to format category. In LOC, both the effect of string length ($t(11) = -5.42$, $p < .001$) and the effect of format ($t(11) = -4.00$, $p < .001$) were significant. VWFA is sensitive to format ($t(11) = -5.42$, $p < .001$), but not to string length ($t(11) = -1.94$, $p = .08$). In the left [digits – words] region, we found a significant main effect of string length ($t(11) = -4.69$, $p < .001$) and of format ($t(11) = -2.30$, $p = .04$). Finally, in the right [digits – words] region, only the effect of string length was significant ($t(11) = -6.29$, $p < .001$).

As summarized in the MDS plots in Figure 2.11, we can conclude that V1 clustered conditions based on the number of characters. In LOC, there was no clear clustering of conditions, there was a sensitivity for both format and string length. In VWFA, we found a clustering based on stimulus category (format). Finally, in the right and left [digits – words] regions we found results similar to those in V1 and LOC, respectively. All these results are visualized on the MDS plots in Figure 2.11.

Table 2.3

Averaged correlational matrices over all subjects, per region of interest

	V1				**LOC**				**VWFA**			
	2L	5L	2D	5D	2L	5L	2D	5D	2L	5L	2D	5D
2L	.41	-.40	.36	-.38	.15	.01	0	-.19	.20	.34	-.26	-.34
5L	-.43	.57	-.55	.39	.02	.31	-.31	0	.34	.68	-.60	-.37
2D	.37	-.54	.58	-.37	.01	-.30	.29	-.01	-.25	-.63	.54	.35
5D	-.35	.38	-.37	.39	-.18	0	-.02	.20	-.34	-.38	.33	.37

	Left [digits – words]				**Right [digits – words]**			
	2L	5L	2D	5D	2L	5L	2D	5D
2L	.43	-.11	.02	-.34	.23	-.09	.08	-.21
5L	-.09	.34	-.16	.02	-.09	.31	-.24	.07
2D	.01	-.17	.13	.01	.07	-.24	.16	-.06
5D	-.35	.02	0	.33	-.22	.09	-.07	.19

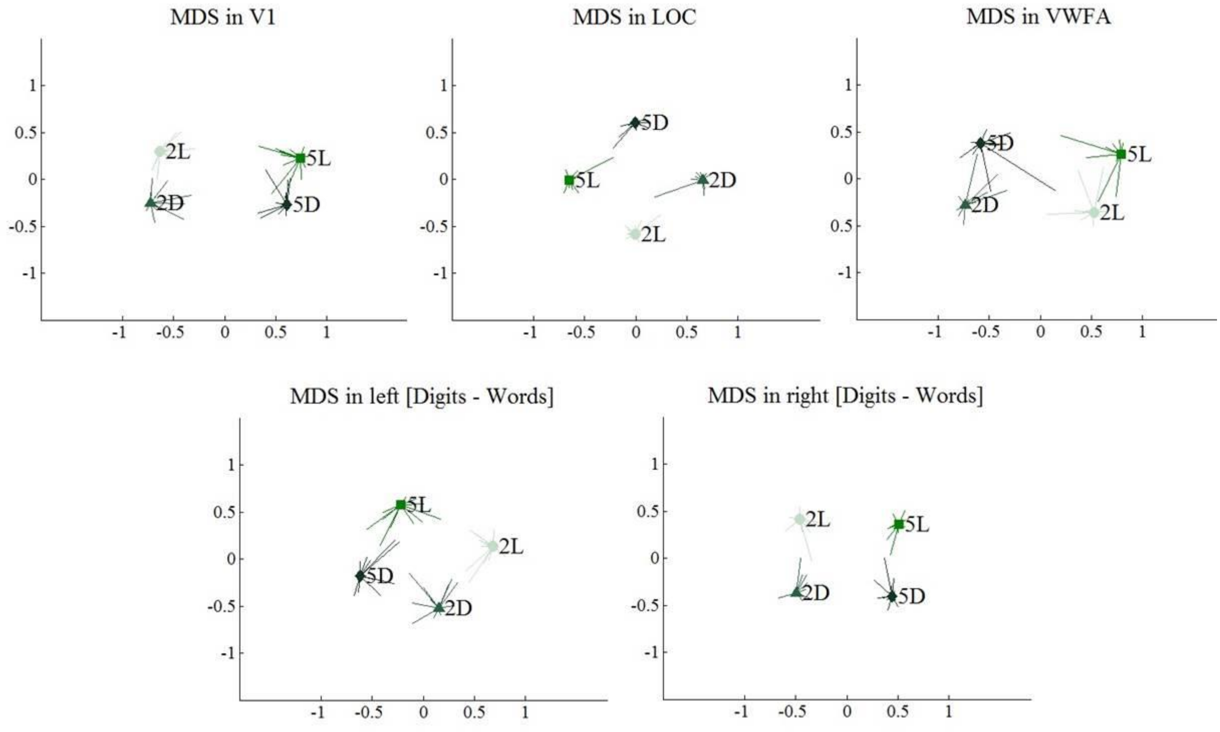

Figure 2.11. Multi-dimensional scaling plots, visualizing similarity between multi-voxel activation patterns for the four included conditions. Light colors represent 2-character strings, dark colors represent 5-character strings. Circles stand for letter strings, triangles for digit strings. Error bars represent the deviation to the mean per individual subject.

2.4 Discussion

The current study served two aims. First, we investigated whether there is a region specifically tuned for Arabic digits that might potentially host the visual code of number processing described in the Triple Code Model (Dehaene & Cohen, 1995, 1997) by contrasting the brain activity elicited by Arabic digits with activity elicited by number words in an arithmetic task. Second, we studied the emergence and formation of this visual code by looking at the evolution of activation patterns throughout the early visual ventral processing stream, more specifically in regions V1, LOC and VWFA.

Two fMRI experiments were conducted. In Experiment 1, participants performed an arithmetic task with subtractions presented in three different formats: Arabic digits, number words and dot arrays. Earlier studies that used subtraction paradigms to investigate the neural correlates of arithmetic have found activation in occipitotemporal areas (for a meta-analysis, see Arsalidou & Taylor, 2011). Similarly, we found a bilateral cluster in lateral occipital cortex that was significantly more active for digits than for number words, which could possibly reflect a region more specifically tuned for digits.

However, the data of Experiment 1 should be treated with great caution. Although we controlled our stimuli for amount of visual information (black pixels) presented, the number of visual elements on the screen varied greatly between digits and number words. This is impossible to control in an arithmetic experiment because number words by definition consist of more visual elements than digits. To ensure that the effects found in Experiment 1 were not due to this difference in visual information, a second fMRI experiment was conducted, in which the number of visual elements presented was controlled for. In Experiment 2, participants were asked to judge the ordering of letter or digit strings, both consisting of either 2 or 5 characters. We reasoned that, if the bilateral [digits – words] region found in Experiment 1 represents a focal region specifically tuned for digits, it should be activated more strongly for digit strings than for letter strings, regardless of string length. However, this was not the case: in both [digits – words] regions: Letter strings elicited more activation than digit strings did. Therefore, the data from Experiment 2 revealed that the region observed in Experiment 1 did not show any preference for digits, at least not in a task-independent and string length-independent manner. This leads us to conclude that the findings of Experiment 1 were either due to task-specific effects, or to visual confounds, and that we did *not* find a region hosting the visual code for digits. At most, one could argue that the activation of these [digits – words] regions would be very much task dependent.

Another limitation which is particularly prominent in Experiment 1 is caused by the differences in behavioral performance between conditions. Because we used block designs in both experiments, it was impossible to discard the incorrectly solved trials in the fMRI analyses. It is well established that erroneous responses elicit additional brain activation in regions associated with performance monitoring, such as the anterior cingulate cortex (Carter et al., 1998; Garavan, Ross, Murphy, Roche, & Stein, 2002). The effect of this increase in brain activity on visual processes in the context of the present study remains unclear. Future studies should therefore attempt to equalize performance levels over all conditions or should employ an event-related paradigm in which it is possible to only analyze brain activity during the correctly solved items.

The current findings might not be in line with the conclusions from previous studies, but could at least suggest a few variables which should be taken into account in future studies. Park et al. (2012) only found a region activated more by numbers than by letters in the right hemisphere using a same/different-task. Pinel et al. (2001) found a region that was more activated for digits than for number words in the context of a number comparison task, located in the right fusiform gyrus, and Pinel & Dehaene (2013) found a region in inferior temporal gyrus that was part of the arithmetic network in the context of a subtraction task. Importantly, none of these studies controlled neither for variability in the number of visual elements presented nor for task-related factors driving the effect, as we did in the present study. It therefore remains uncertain if the visual regions described in these previous studies are specifically involved in the processing of the visual code.

A study by Shum et al. (2013) suggests that there might be a focal region with a task-independent preference for digits over number words, but that typical fMRI studies, such as the current one, do not have the sensitivity to detect this region. Shum et al. (2013) used intracranial electrophysiological recordings, and found a region in the inferior temporal gyrus that responded more to digits compared to morphologically, phonologically and semantically similar symbols (Shum et al., 2013). This possible *visual number form area* was located in a 3T MRI signal drop-out zone, which might explain why we were not able to pick it up using fMRI in healthy adults. Indeed, we inspected our fMRI images and had signal drop-out at the coordinates reported by Shum et al. (2013). However, a recent study by Abboud, Maidenbaum, Dehaene, & Amedi (2015) reported a number form area in congenitally blind and sighted adults that was located in the right inferior temporal gyrus [53, -44, -12], near the region reported by Shum et al. (2013), but outside of this signal drop-out zone. This region is located far more anteriorly than the region we found in Experiment 1. However, the subject sample, the complex stimuli, and the categorization task Abboud and colleagues used are very different from our sample, stimuli and subtraction task, making it difficult to compare both studies.

It has been debated in the fMRI literature to what extent it is fruitful to focus exclusively upon small focal regions with a clear preference for a particular stimulus condition, and ignore the large parts of cortex, which are also activated by this condition without a clear preference for other conditions (see e.g., Haxby et al., 2001; Spiridon & Kanwisher, 2002). A second aim of this study was therefore to investigate the emergence of the visual code along the ventral visual processing stream in regions, which might differentially process the different symbolic numerical formats (i.e., digits and number words). We did this by comparing patterns of activation of the four conditions of Experiment 2 in five regions of interest along this visual processing pathway: V1, LOC, VWFA, and the two [digits – words] clusters found in Experiment 1.

In V1, digits and letters of the same string length were clustered, suggesting that V1 clusters stimuli based on amount of visual information. In LOC and in both [digits – words] clusters, we found a less clear picture: all conditions appeared to be represented distinctly with no clear clustering. Nevertheless, each of the ROIs was sensitive to the different conditions. Most strikingly, the left [digits – words] cluster, which was activated similarly by all four conditions according to univariate analyses, still differentiated digit strings from letter strings (see Table 2.3). Thus, despite the absence of a focal region preferring digit strings over letter strings, there is clear evidence for a distributed selectivity for the difference between digits and letters. This selectivity is most striking in the VWFA, where it is accompanied by a focal preference of the whole region for letters over digits (Cohen & Dehaene, 2004; Polk et al., 2002; Reinke, Fernandes, Schwindt, O’Craven, & Grady, 2008). The representations in VWFA make a categorical distinction between digits and letters and mostly ignore the large physical difference between a two-character and a five-character string.

2.5 Conclusion

Based on the results of both Experiment 1 and Experiment 2, we suggest that there is an alteration in representations throughout the ventral processing stream from clustering based on amount of visual information towards clustering based on symbolic stimulus category, as found previously for objects in general (Op de Beeck, Haushofer, & Kanwisher, 2008). The emerging selectivity for the two symbolic formats, digit versus letter strings, is focal to a certain extent, with task-independent preference for letters over digits in the VWFA and possibly a task-dependent preference for digits over number words in lateral occipital cortex. The emerging selectivity is also distributed across regions, which do not have an overall preference for one format over the other.

CHAPTER 3

Brain activity during arithmetic in symbolic and non-symbolic formats in 9-12 year old children

Published as

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Abstract

People process numbers in different formats, such as dot arrays (non-symbolic), Arabic digits and number words (symbolic), and use these representations when performing arithmetic calculations. It remains, however, unclear if and how these various presentation formats affect brain activity during arithmetic. We conducted an fMRI study in 23 typically developing children aged 9 to 12. The children were asked to subtract numbers up to 10 and compare the result to a reference number. Numbers were presented in non-symbolic (dot arrays), as well as symbolic formats (Arabic digits and number words). Our findings suggest that similar brain networks are recruited during arithmetic with different symbolic formats, i.e., Arabic digits and number words. On the other hand, there are clear differences between calculating with symbolic and non-symbolic formats. Specifically, calculating in symbolic formats showed increased activity in angular and supramarginal gyri, whereas arithmetic in the non-symbolic format showed increased activity in middle occipital and superior parietal lobes, as well as in superior frontal gyrus and insula. These differences in brain activity might be explained by differences in the strategies used to solve these arithmetic problems.

3.1 Introduction

We deal with numerosity and arithmetic every day. We set dates and times for meetings, and adjust recipes for the appropriate number of people. Moreover, this numerical information can be presented to us in various formats. The number of objects (non-symbolic format) can be used to represent numerical information (e.g., the number of red peppers on a menu represent spiciness, the number of stars represent hotel quality), but on the other hand, culturally devised symbolic formats (e.g., Arabic digits, number words), are used to grade exams or to measure the speed of a car. Both formats are used when doing arithmetic.

Arithmetic has been studied intensely in the past, but mostly in adult samples. The most commonly used theoretical framework used in these adult studies, is the Triple Code Model (Dehaene & Cohen, 1997). According to this model, numerical information can be represented in three distinct codes, which all play a (distinct) role during arithmetic. First, there is the magnitude code, which has received the largest research attention to date. This code is located in the bilateral intraparietal sulci and is activated when individuals have to estimate, compare or manipulate the magnitudes of numbers or have to perform calculations where the magnitudes of the numbers are relevant, as is the case during subtraction. Second, and far less investigated (see Menon, 2015, for a discussion), there is a visual code, which is involved in processing Arabic number forms during number processing and arithmetic. This process takes place in the bilateral inferior ventral occipitotemporal areas. Third, there is a verbal code in which numbers are phonologically represented. This code is located in the left temporoparietal language-related areas, which are also involved in accessing memory of arithmetic facts (e.g., Grabner et al., 2009). The Triple Code Model further proposes two routes via which arithmetic happens (Dehaene & Cohen, 1997). There is a direct route, when solutions are retrieved as facts from verbal long-term memory, mainly during multiplication. This route has been linked to the verbal code located in the left temporoparietal language-related areas. The indirect route, on the other hand, is used when the solution to a problem cannot be immediately retrieved from memory and a procedural manipulation, potentially relying on the magnitude code, is needed. During such strategies, individuals might, for example, decompose a problem into smaller problems (e.g., 15 – 7 =, 7 is split into 5 and 2, which allows one to calculate 15 – 5 – 2 = 10 – 2 = 8), which requires a manipulation of the magnitudes in the problem, but also draws on additional working memory resources. Importantly, this Triple Code Model has been developed and tested using adult data and

represents the end-stage of development. As a result, it is not necessarily generalizable to children (Ansari, 2010).
Surprisingly few studies have examined brain activity during arithmetic in children. In a recent meta-analysis (Kaufmann et al., 2011), reported that children mainly recruit frontal, parietal and ventral temporal areas, and that brain activity is moderated by competence level, task difficulty and used strategy. Specifically, this analysis indicated an increase in (intra)parietal activity during the use of procedural strategies (indirect route), suggesting the involvement of the magnitude code, and an increase in ventral temporal activity during fact retrieval (direct route), pointing to an involvement of the verbal code.

More recently, Prado, Mutreja, & Booth (2014) contrasted brain activity during subtraction and multiplication and observed increased right inferior parietal activity during subtraction, and increased left temporal activity during multiplication; a similar pattern of findings was observed in adults (Prado et al., 2011). These differences coincide with the direct/indirect routes predicted by the Triple Code Model and suggest that different calculation strategies (fact retrieval during multiplication vs. magnitude-based procedural calculation during subtraction) recruit different brain areas.

All fMRI studies on arithmetic in children have so far solely used Arabic digits as their stimuli, leaving it unresolved as to what the effect of the use of this presentation format is. In the current study, we therefore included another symbolic format (number words), as well as a non-symbolic format (dot arrays), to gain insight into the recruitment of all three codes described in the Triple Code Model during arithmetic. We designed an fMRI paradigm in which children were asked to subtract numbers up to 10 presented in various formats. We focused on subtraction, to allow for more variation in the possible strategies used for solving the arithmetic problems. Against the background of behavioral data in children of the same age (Vanbinst et al., 2015), we expected that problems presented as digits would be retrieved from memory and consequently, would activate left temporoparietal areas (verbal code). For problems presented as number words, we expected additional activity in areas associated with the processing of words, such as visual word form area (Cohen & Dehaene, 2004; McCandliss, Cohen, & Dehaene, 2003). Finally, we expected that subtraction problems presented as dot arrays would draw heavily on the magnitude code, and therefore we predicted a particular increase in bilateral intraparietal sulcus activity (magnitude code), compared to the other conditions. To be able to better interpret the neural results, we additionally conducted a behavioral study in which we recruited a new sample of children of the same age range, who all did the same calculation task, but who additionally had to verbally report on a trial-by-trial basis how they solved each problem. Such trial-by-trial verbal reports are a reliable and valid way to assessing children's strategy use (Siegler & Stern, 1989), and can therefore validate that children in fact use the strategies we expect them to. Because these trial-by-trial verbal protocol data are very difficult to acquire in the scanner, and because we wanted to avoid retesting effects, these data were collected in a new sample.

3.2 Materials and Methods

3.2.1 Participants

Twenty-three typically developing children (12 male) aged between 9 and 12 years old (*M* = 10.73 years, *SD* = 0.87) participated in the fMRI study. One child was further discarded due to excessive movement in the scanner (see below). Five children were left-handed. All participants were recruited via primary schools in the vicinity of Leuven (Belgium), had normal or correct-to-normal vision, and reported no history of neurological or psychiatric illness. Participants' parents or legal guardians gave written consent prior to taking part in the study. Children were paid for their participation. The study was approved by the Medical Ethical Committee of KU Leuven. To test whether the arithmetic and reading abilities as well as intelligence of the participants were within normal range, standardized tests were administered (see below). None of the participating children were diagnosed with learning disorders and none received remedial interventions. Our analyses indicate that all of the children had average to above-average intelligence. The average scores on the arithmetic and reading tests were all in the normal range, yet low minimum and high maximum scores include both low and high achievers and indicate that our sample reflects the broad variability in the general population (see Table 3.1). Furthermore, 37 children (17 male) of a comparable age (*M* = 10.36 years old, *p* = .07) participated in the behavioral study. They were recruited via a local primary school. Again, none of these children were diagnosed with learning disorders and none received remedial interventions.

Table 3.1

Results of standardized tests.

Test	*M*	*SD*	Min.	Max.
TTA	4.55	3.10	1	10
OMT	8.00	3.02	1	14
Klepel	10.09	2.16	7	15
Block Design	13.09	2.65	9	18
Vocabulary	11.86	2.31	9	19

Note. Decile scores are reported for the Tempo-Test Arithmetic, for all other tests standard scores are reported.

3.2.2 Imaging study

3.2.2.1 fMRI task

In the fMRI task, children performed a subtraction task that was similar to the one used in Peters, De Smedt, & Op de Beeck (2015). Children had to subtract two numbers below 10, and had to decide whether or not the result was equal to a reference magnitude, which was either four or five (depending on the run). The format in which the subtraction items were presented was manipulated (dot arrays, Arabic digits or number words). The design of this experiment is illustrated in Figure 3.1.

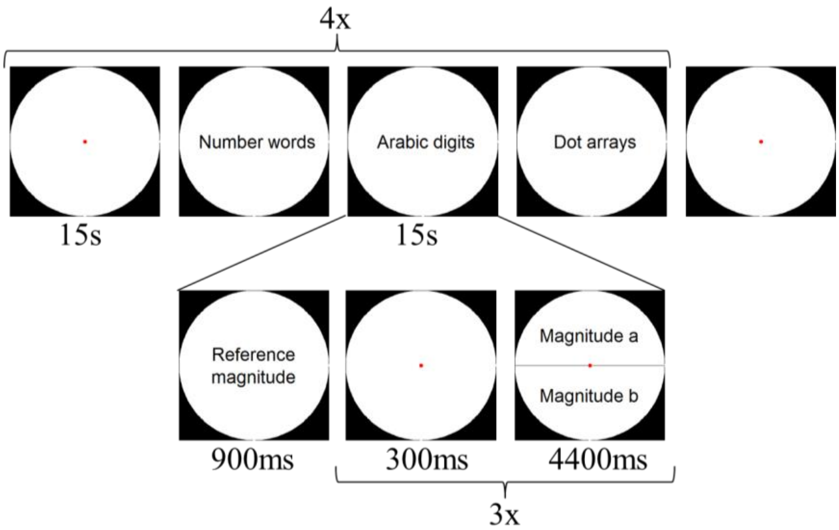

Figure 3.1. Schematic overview of a possible design of the subtraction task.

Stimuli were presented in a white circle on a black background. The circle was divided into two halves by a horizontal black line. The magnitude in the lower half of the circle had to be subtracted from the magnitude in the upper half (see Figure 3.2). Subtraction items presented as dot arrays were created via a Matlab script (Dehaene et al., 2005), controlling for parameters such as item size, total area and luminance. For subtraction items presented as Arabic digits and number words, an adapted version of the Matlab script by Dehaene et al. (2005) was used, in which the amount of visual information (i.e., the number of black pixels) presented was controlled by varying font size. Participants answered by pressing one of two response buttons on a response box.

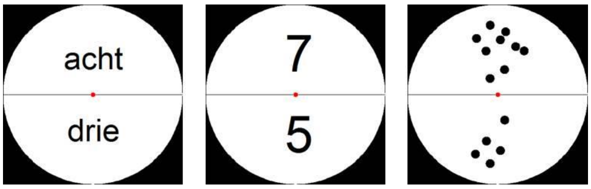

Figure 3.2. Examples of stimuli presented as number words, Arabic digits and dot arrays.

Each fixation block, as well as each format block lasted 15 seconds. The ordering of the format blocks followed a symmetrical structure; items in the first and last block were presented in the same format, the same holds for the second and penultimate block, etc. Within each format block, participants were first presented with the reference magnitude in the appropriate format (900ms), followed by three trials consisting of a fixation stimulus (300ms) and the subtraction item (4400ms). In total, each participant performed 4 runs of 255 seconds each. The change in reference magnitude over runs followed a fixed order ([4 5 4 5]) and was implemented to ensure sufficient variation in the task.

3.2.2.2 Imaging parameters

Imaging data were collected via a 3T Philips Ingenia CX Scanner, located at the Department of Radiology of the University Hospital in Leuven, with a 32-channel head coil and an EPI sequence (52 slices, 2.19 x 2.19 x 2.2 mm voxel size, interslice gap 0.3 mm, TR = 3000 ms, TE = 29.8 ms, flip angle = 90 degrees, 96 x 95 acquisition matrix). A high-resolution T1-weighted anatomical image (182 slices, resolution 0.98 x 0.98 x 1.2 mm, TE = 4.6 ms, 256 x 256 acquisition matrix) was acquired for each participant. Stimuli were displayed using PsychToolbox 3 (Brainard, 1997) and presented via an NEC projector onto a screen located approximately 46 cm from participants' eyes, which was visible via a mirror attached to the head coil.

3.2.2.3 Standardized tests

To assess arithmetic ability, the Tempo-Test Arithmetic (TTA; De Vos, 1992) was administered. The TTA is a paper-and-pencil task in which children were asked to solve arithmetic problems with increasing difficulty in all operations (addition, subtraction, multiplication, division and a mixture of all), with a time limit of one minute per operation. The number of correctly solved items per operation was registered. Reading ability was tested using the One-Minute Test (OMT; Brus & Voeten, 1979) and the Klepel (Van den Bos, Spelberg, Scheepstra, & De Vries, 1994). In the One-Minute Test, the number of words children could read aloud correctly within one minute was registered. For the Klepel, children read aloud non-words, and the time limit was set to two minutes. Finally, to get an indication of IQ, two subscales of the Dutch Wechsler Intelligence Scale for Children, Third Edition (WISC-III-NL; Kort et al., 2005) were administered: Block Design and Vocabulary. These tasks tap into performance and verbal intelligence, respectively.

3.2.2.4 Procedure

The imaging study consisted of two sessions. In a first session, all standardized measures were collected, and the children were familiarized with the task they would do and with the procedure associated with an MR scanner via a mock scanner. In the second session, the children came to the Department of Radiology at the University Hospital in Leuven, where structural and functional images were collected.

3.2.3 Behavioral study

The children who participated in the behavioral study, performed the fMRI task outside the scanner, and reported on a trial-by-trial basis how they solved each problem. Their responses were classified into four categories: procedural strategies, retrieval, guessing and a rest category. Furthermore, we assessed their arithmetic ability using the TTA, and reading ability using the OMT, and their performance did not differ from the children who participated in the fMRI experiment (see Appendix A, Table 1). Below, we will only discuss the strategy reports of these children, yet a detailed overview of all behavioral data as well as a comparison of both participant groups is included in Appendix A.

3.2.4 Analyses

3.2.4.1 Behavioral analyses

All behavioral data were analyzed using SPSS (IBM SPSS Statistics 22; IBM Corp., Chicago, IL, USA). To control for multiple comparisons, a Bonferroni correction was applied, by multiplying each specific *p*-value by the number of contrasts calculated in that analysis. The alpha-criterion therefore remained .05.

3.2.4.2 fMRI preprocessing and analyses

All imaging data were preprocessed using the Statistical Parametric Mapping software package (SPM8, Wellcome Department of Cognitive Neurology, London). To control for excessive motion during scanning, all runs in which participants moved more than one voxel size (2.2 mm) on two consecutive images were discarded. Subjects with less than two runs without excessive movement, were discarded in all analyses on the imaging data. This criterion led to the discarding of one male participant, leading to a final sample of 22 participants. Of the other subjects, 4.55% of the runs were discarded.

Functional images were corrected for slice-timing differences, and for head motion artifacts by realigning all images to the first image. Functional images were coregistered to the anatomical image. Both functional and anatomical images were normalized to the standard Montreal Neurological 152-brain average template, and finally, functional images were smoothed using a Gaussian kernel of 10 mm full-width at half maximum (FWHM). The effect of the experimental conditions per voxel was estimated by creating a general linear model per participant. Motion realignment parameters were also included as regressors in the general linear models, to further control for variation due to movement artifacts. Finally, a second-level group analysis was performed on all pairwise contrasts between the three format conditions and fixation, and we looked at activation on a whole brain level (threshold of $p < .05$ after family wise error correction).

3.3 Results

3.3.1 Behavioral results during fMRI acquisition

Participants' accuracy scores and reaction times were averaged over all runs. Mean accuracy and reaction time over all participants is shown in Table 3.2. A one-way repeated measures ANOVA with format (dots vs. digits vs. words) as within-subject factor was performed on the accuracy scores and on the reaction times. Concerning the accuracy scores, the ANOVA showed a significant main effect of format ($F(2,42) = 55.09$, $p < .001$). Calculated contrasts indicated that the accuracy scores in the dot format were significantly lower than in the digits and word formats (both *p*'s < .001). The accuracy scores in the digits and words conditions did not differ significantly ($p = .10$). The analysis on the reaction time data showed a main effect of format ($F(2,42) = 55.85$, $p < .001$). Subsequent contrasts showed that the response to subtraction items presented as digits were fastest, followed by words and dots (all *p*'s < .001).

Table 3.2

Behavioral results of the subtraction task during fMRI imaging

	% Correct	*SD*	RT (ms)	*SD*
Dot arrays	80.85	10.11	2453	516
Arabic digits	97.82	3.34	1555	330
Number words	95.74	3.82	1821	344

3.3.2 Additional behavioral results

In the additional data we collected, the effect of format was similar to the one reported in 3.3.1 (see Appendix A). These data further clearly showed that most of the problems presented as dot arrays (77.85 %, 566/727 items) were solved using procedural strategies (mainly counting) and retrieval strategies were never used. On the other hand, the majority of problems presented as Arabic digits (96.79 %, 966/998 items) and numbers words (96.34 %, 948/984 items) were indicated to be retrieved from memory.

3.3.3 Imaging results

For exploratory purposes, we first performed whole brain group level analyses for each format condition versus fixation, in order to get a broad overview of all regions involved in calculation (see Appendix B).

In the exploratory analysis, a visual inspection of the whole brain analyses comparing each format to fixation showed a similar pattern of findings for every condition. For all formats, increased activity in bilateral occipital regions, superior and inferior parietal lobules, cingulate cortex and anterior insula (left-lateralized for digits, bilateral for number words and dots) was observed. Number words showed increased activity in the fusiform gyrus (visual word form area) and right inferior frontal gyrus. Dot arrays as well as number words showed increased activity in the bilateral medial frontal gyrus and precentral gyrus (left for words, bilateral for dots).

In a second step, we directly and statistically tested differences between stimulus formats by calculating all pairwise contrasts (digits vs. dots; digits vs. words; words vs. dots), in which one format served as active baseline control for the other format. A detailed overview of the regions that were significantly more active in one compared to the other format, is presented in Table 3.3.

Table 3.3

Region, coordinates of the peak voxel, number of voxels (k) and t-value of activation clusters elicited by the contrasts digit vs. words, dots vs. digits and dots vs. words. Only clusters consisting of more than 20 active voxels are mentioned.

Region	**x**	**y**	**z**	**k**	***t***
[Digits – Words]					
/					
[Words – Digits]					
Left Inferior Occipital Gyrus	-20	-95	-8	803	11.50
Right Inferior Occipital Gyrus	24	-100	-6	420	12.23
[Dots – Digits]					
Right SPL, MOG & Cerebellum	14	-68	68	7724	14.56
Left SPL & MOG	-26	-98	-2	3840	17.06
Cerebellar Vermis + Left Cerebellum	-2	-76	-30	3598	14.93
Left & Right SMA & MCC	0	16	52	1212	9.23
Right Anterior Insula Lobe	34	22	6	894	11.11
Left Anterior Insula Lobe	-40	14	2	357	10.81
Right Superior Frontal Gyrus	30	-4	66	341	10.45
Right Precentral Gyrus	50	2	36	201	7.27
Left Superior Frontal Gyrus	-24	-4	66	180	8.35
Right Middle & Superior Orbital Gyrus	26	44	-14	23	7.91

[Dots – Words]					
Left & Right SPL + Right MOG	36	-86	28	7533	18.73
Left Cerebellum	-2	-78	-30	597	11.20
Right Anterior Insula Lobe	34	18	4	520	9.99
Right Superior Frontal Gyrus	30	-2	62	407	9.96
Left Cerebellum	-26	-66	-28	383	10.09
Left Anterior Insula Lobe	-38	16	4	248	10.18
Right Cerebellum	30	-54	-36	226	9.05
Left MOG	-48	-82	4	205	10.53
Left SFG & Precentral Gyrus	-24	-6	64	124	7.61
Right Supplementary Motor Area	8	16	52	100	7.55
[Digits – Dots]					
Left Angular Gyrus	-52	-70	40	204	7.75
Right Supramarginal Gyrus	60	-26	22	174	7.40
Left & Right Mid Orbital Gyrus	2	50	-10	166	7.10
Right Angular Gyrus	60	-66	34	54	9.30
Left Precuneus	-4	-56	20	53	7.03
Left Cuneus	-4	-94	28	49	7.46
[Words – Dots]					
Left & Right Cuneus & Precuneus	4	-76	34	936	9.97
Right Mid Orbital Gyrus	2	50	-10	412	9.26
Left IPC & Middle Temporal Gyrus	-68	-50	12	259	8.75
Right IPC & Angular Gyrus	60	-64	34	195	10.68
Right Supramarginal gyrus	60	-28	24	38	6.84

Note. MOG = middle occipital gyrus, MCC = middle cingulate cortex, SPL = superior parietal lobule, SFG = superior frontal gyrus, SMA = supplementary motor areas, IPC = inferior parietal cortex.

Only very few differences between the two symbolic formats (digits and number words) were observed: *No* voxels were significantly more active for digits than for words; the reverse contrast only revealed differences in primary visual cortex (see Figure 3.3).

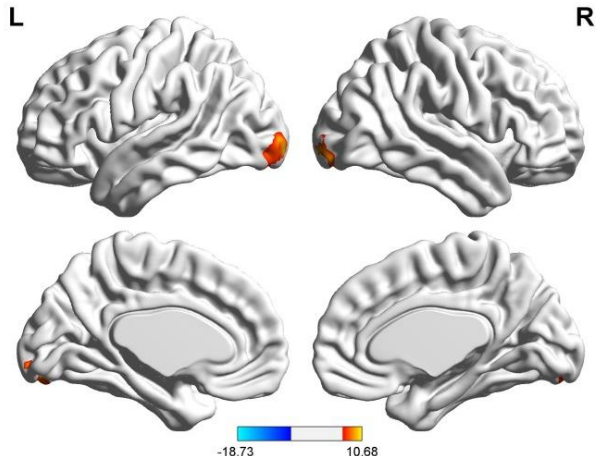

Figure 3.3. Visualization of the contrast [Words – Digits]. Activation spots in red indicate regions that were more activated by words than by digits. This contrast was visualized using BrainNet Viewer (Xia et al., 2013).

However, there were large differences in brain activity when contrasting non-symbolic (dot arrays) with symbolic formats (Table 3.3; see also Figures 3.4 and 3.5). Non-symbolic items elicited more activation in the bilateral superior parietal lobule (including the intraparietal sulcus), middle occipital gyrus, cerebellum, insula lobe and superior frontal gyrus compared to symbolic items. In addition, bilateral middle cingulate cortex and right middle and superior orbital gyrus were activated more by arithmetic problems presented as dot arrays, than as Arabic digits. On the other hand, calculation in symbolic formats showed larger activity in the bilateral angular gyrus, right supramarginal gyrus, right mid orbital gyrus, left cuneus and precuneus compared to non-symbolic stimuli. Furthermore, the left angular gyrus and left mid orbital gyrus were activated more by digits than by dots, and the left middle temporal gyrus and right cuneus and precuneus were activated more by number words than by dots.

To further statistically test the similarities/differences between the different formats, we ran an additional analysis in which we directly compared the beta weights of the abovementioned pairwise contrasts (digits vs. dots; digits vs. words; words vs. dots). This analysis was done in a stepwise way in order to avoid circular analyses (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009).

First, we looked at the [Digits – Dots] contrast. This contrast revealed three regions: left angular gyrus, right angular gyrus and right supramarginal gyrus (see Table 3.3). In these regions, we extracted the mean beta value for each condition. We then ran a within-subject ANOVA on each of these beta weights, and looked at the pairwise contrasts on which this contrast was *not* based (e.g., digits vs. words and dots vs. words in the [Digits – Dots] contrast), to avoid circular testing (Kriegeskorte et al., 2009). By definition, digits activate these regions more than dots do, be it that we find negative beta values (see boxplots in Figure 3.4). However, also number words show higher activation levels than dot arrays (all p's < .001), in regions originally activated by Arabic digits. The difference in activation between number words and digits was not significant in either of the three regions (all p's > .90).

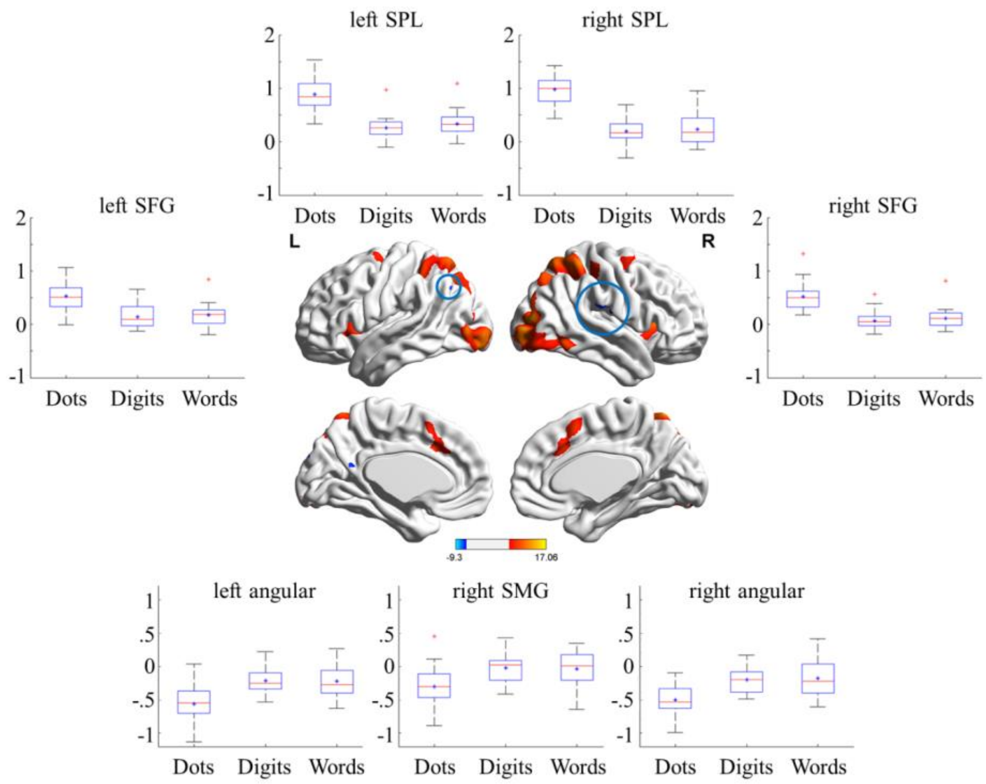

Figure 3.4. Visualization of the contrast [Dots vs. Digits]. Activation blobs in blue indicate regions that were activated more by digits, activation blobs in red indicate regions that were activated more by dot arrays. Boxplots show the mean activation over subjects for all three conditions in seven key regions. Regions at the top of the figure are activated more by dot arrays, regions at the bottom more by Arabic digits. This contrast was visualized using BrainNet Viewer (Xia et al., 2013). *Note*. SFG = superior frontal gyrus, SPL = superior parietal lobule, angular = angular gyrus, SMG = supramarginal gyrus.

The same rationale was followed for regions activated more by dots than by digits. We delineated left and right superior frontal gyrus (SFG), and left and right superior parietal lobule (SPL). As both left and right SPL were part of a larger activation cluster, we used an anatomical mask (WFU PickAtlas, embedded in SPM8), and selected the activated voxels that were located within the left and right SPL. We then subsequently ran a within-subject ANOVA in each region on the extracted beta weights. Crucially, we only looked (to avoid circular testing) at the difference between number words and dots, which was significant for each of these regions (all p's < .001), and at the difference between number words and digits, which was not significant (all p's > .12) in these regions. The results for contrast [Words – Dots] and [Dots – Words] show exactly the same pattern of findings, with dots consistently showing different levels of activation than both symbolic formats, which do not differ from each other. Again, the mean beta values in regions activated more by words than by dots are negative (see boxplots in Figure 3.5).

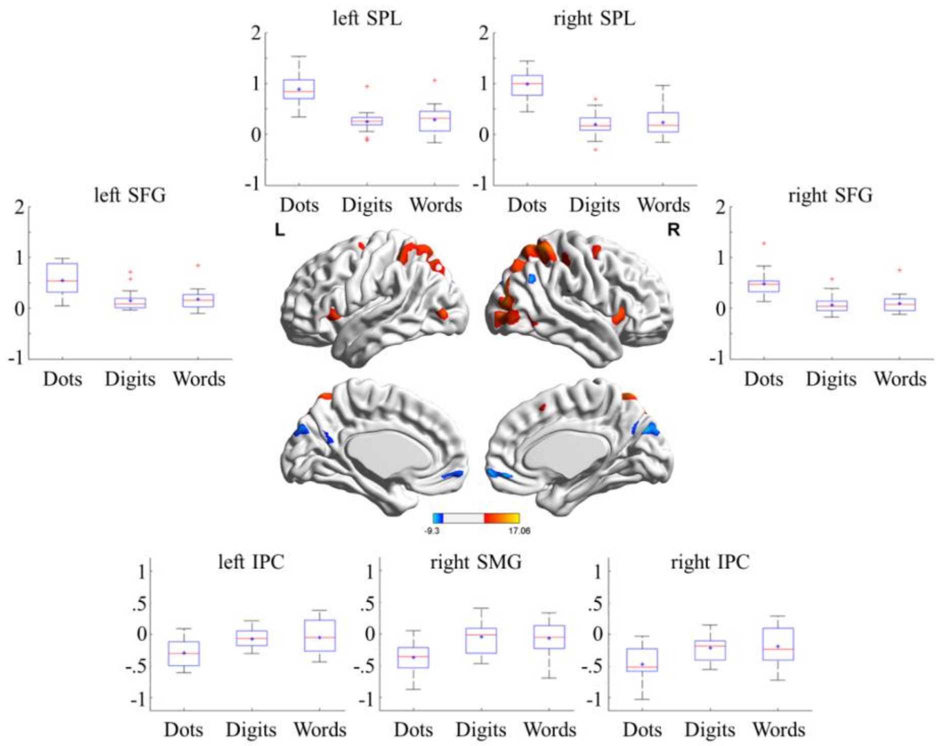

Figure 3.5. Visualization of the contrast [Dots vs. Words]. Activation blobs in blue indicate regions that were activated more by number words, activation blobs in red indicate regions that were activated more by dot arrays. Boxplots show the mean activation over subjects for all three conditions in seven key regions. Regions at the top of the figure are activated more by dot arrays, regions at the bottom more by number words. This contrast was visualized using BrainNet Viewer (Xia et al., 2013). *Note*. SFG = superior frontal gyrus, SPL = superior parietal lobule, IPC = inferior parietal cortex, SMG = supramarginal gyrus.

These analyses show that the brain activity during Arabic digits and number words was very similar, as their mean activation is not significantly different in either of the regions we delineated. By contrast, these symbolic formats differ significantly from the dot arrays, again in all delineated regions. These results show that the neural networks involved in calculation using symbolic formats are very similar, and that there are distinct differences in the regions activated by calculation using symbolic vs. non-symbolic formats.

3.4 Discussion

The aim of this study was to investigate brain activity during calculation in symbolic (Arabic digits, number words) and non-symbolic (dot arrays) presentation formats. All three format conditions activated occipitoparietal regions, insula lobe and cingulate cortex. We also found additional activity in fusiform gyrus (i.e., visual word form area) for number words. In a similar study in adults (Peters et al., 2015), we observed that activity in visual word form area was higher for number words than for digits and dot arrays. However, in this study we only found additional visual word form area activity for number words versus fixation, rather than versus dot arrays or Arabic digits. Finally, dot arrays elicited more brain activation in frontal regions, possibly reflecting increased reliance on working memory and attention processes (see Kaufmann et al., 2011).

The directly comparison of the three formats to each other indicated that both symbolic formats recruit the same neural regions, with the exception of additional primary visual cortex activation for number words. This however, can be explained by the visual properties of the stimuli used: number words are by nature more complex visual stimuli, consisting of more visual elements (lines and individual characters) than Arabic digits.

More importantly, symbolic arithmetic problems elicited a different pattern of brain activation than non-symbolic problems. Specifically, symbolic problems elicited more activation in bilateral angular and supramarginal gyri, whereas non-symbolic problems showed increased activity a broader network, including bilateral superior parietal lobule, intraparietal sulcus, middle occipital gyrus, superior frontal gyrus, insula and cerebellum. These two networks seem to coincide with the direct and indirect routes and their neural correlates as described by Dehaene and Cohen (1997; see also Dehaene et al., 2003). It is important to acknowledge that the activation differences between the different formats are probably not due to the fact that subjects had to compare the result of the subtraction exercise to the provided reference magnitude. This is because the abovementioned activation differences reflect the direct comparison of two formats, which cancels out the comparison process that is required in each format condition.

These differences in networks between symbolic and non-symbolic formats might reflect the use of different calculation strategies, i.e., fact retrieval in symbolic formats (direct route), and magnitude-based procedural strategies in the non-symbolic format (indirect route), as postulated by the Triple Code Model (Dehaene & Cohen, 1997, but see also Prado et al., 2014). The results from the additional behavioral data indeed confirm this interpretation. Children of a similar age and ability level solved symbolic problems with fact retrieval, and non-symbolic problems with procedural strategies, as indicated by trial-by-trial verbal reports.

Our findings are in line with previous studies who suggested that procedural strategies rely on a bilateral frontal and superior parietal network, whereas retrieval strategies activate temporo-parietal regions (De Smedt, Holloway, & Ansari, 2011; Grabner et al., 2009; Menon, 2015; Prado et al., 2014). It is, however, important to emphasize that various earlier brain imaging studies (see e.g., Grabner et al., 2009; Prado et al, 2014), as well as the Triple Code Model (Dehaene & Cohen, 1995, 1997), observed that the brain activity during fact retrieval was left-lateralized, whereas in the current study we observe bilateral increases in temporoparietal activity during these problems. Importantly, Arsalidou & Taylor (2011) pointed out in their meta-analysis of brain activity during calculation in adults, that also the right angular gyrus plays a role during arithmetic, and suggested to include the right angular gyrus, among other regions, in the Triple Code Model. This meta-analysis was based on adult data and it remains to be determined to which extend these findings can be generalized to children. Interestingly, previous studies with similar tasks in children also found activation in right inferior parietal areas and in the right supramarginal gyrus (Evans, Flowers, Napoliello, Olulade, & Eden (2014), which is very similar to the current results. Furthermore, a meta-analysis by Kaufmann et al. (2011) also revealed right angular gyrus and right inferior parietal cortex activation during calculation. These data suggest that brain activity during arithmetic fact retrieval in children might not be as left-lateralized in the temporoparietal cortex, as is observed in adults.

It is true that Prado et al. (2014) observed in children activation increases during fact-retrieval tasks that were left-lateralized in the temporoparietal cortex. However, different from the current study, Prado et al. (2014) used an ROI approach with functional localizers in which they delineated left temporal cortex and left inferior frontal gyrus with a phonological task, and the right intraparietal sulcus and right posterior superior parietal lobule with a number comparison task. In the current study, we did not use such an ROI approach, but investigated our contrasts at the whole brain level. It remains unknown whether in Prado et al. (2014) other regions, beyond those that were delineated as ROI, were consistently more active during calculation, for example, right-hemisphere analog regions during the arithmetic fact retrieval items, as we currently observe. In all, this issue of the lateralization remains unclear (in children) to date, and should therefore be investigated more thoroughly in future research that would ideally focus on the development of this lateralization over time, potentially using a longitudinal design.

We would like to highlight that previous studies on brain activity during calculation investigated the effects of strategy use by contrasting different operations (e.g., multiplication to investigate fact retrieval; subtraction to investigate procedural strategies, see Prado et al., 2014). On the other hand, we reported differences in strategy use *within* one operation, namely subtraction. This indicates that it is the strategy but not the operation itself that determines brain activity. These strategies are determined by specific characteristics of an arithmetic problem, such as the presentation format or and people’s familiarity with a specific problem.

An alternative explanation for the current results might lie in task load, i.e., in how demanding a certain task is. As mentioned above, the regions activated more by digits/words compared to dots have been described as being part of the default mode network (Raichle et al., 2001). Regions within this default mode network increase in activation as cognitive demands decrease. On the other hand, the regions activated more by dots than by digits/words are very similar to the regions described as being part of a multiple-demand network (Fedorenko, Duncan, & Kanwisher, 2013). This multiple-demand network is a network activated by cognitive tasks, independent of the specific content or task at hand. The more demanding the cognitive task, the higher the activity in this network. Because calculation with digits or number words was easier, as is evidenced by our behavioral data, and therefore less cognitively demanding than calculation with dot arrays, our results also fit within the framework of these networks. This alternative interpretation has been generally overlooked within the literature of numerical cognition (e.g., Prado et al., 2014) and should be considered more thoroughly in future research.

This study also faces certain limitations. First of all, it is important to note that the age range of the participants was substantial and future studies should try to investigate the effect of formats in a sample of a more narrow age range. It is also important to emphasize that the accuracy differed between the symbolic and non-symbolic presentation formats, i.e., non-symbolic items were solved significantly worse than symbolic problems. This difference in task difficulty might explain the current findings to some extent, yet it is important to keep in mind that procedural strategies will always be less accurate (and slower) compared to retrieval strategies, even in very simple arithmetic problems (e.g., Vanbinst et al., 2015), which makes procedural strategies a priori more difficult than retrieval strategies. Because we used a block design, the incorrect trials could not be discarded from our analyses. Incorrect responses are known to activate an error network, including regions such as the cingulate cortex (which in fact was activated more by exercises presented as dot arrays than by items presented as Arabic digits, see Table 3.3) (Carter et al., 1998; Garavan et al., 2002). Future studies might benefit from using an event-related paradigm, as incorrectly solved trials could then be analyzed separately. Finally, the current task was very specific and only included magnitudes 1 to 9. It remains to be determined how this pattern of findings changes when larger magnitudes are used in the task, as calculation with these larger magnitudes might result in a larger variety of strategies (see e.g., Peters, De Smedt, Torbeyns, Ghesquière, & Verschaffel, 2013) and thereby might recruit the observed networks in different ways. Future studies should investigate these possibilities.

The fMRI experiment in the current study might be an interesting task paradigm to study arithmetic in children with learning disorders such as dyscalculia or dyslexia. Indeed, fMRI studies with both groups of children have shown that both conditions are associated with abnormal brain activity patterns during (symbolic) calculation (Berteletti et al., 2014; De Smedt et al., 2011; Evans et al., 2014). It has been suggested that children with dyscalculia have problems in the representation of numbers (see De Smedt, Noël, Gilmore, & Ansari, 2013, for a review). Furthermore, children with dyslexia have problems with phonology (Mccardle, Scarborough, & Catts, 2001; Stanovich et al., 1994), making it plausible that their reported arithmetic problems, both behaviorally (De Smedt & Boets, 2010) and at a neural level (Evans et al., 2014), originate from problems with the verbal code (for a review, see Ashkenazi, Black, Abrams, Hoeft, & Menon, 2013). Because our paradigm appears to be sensitive enough to pick up the use of different strategies in different codes, it might be a fruitful design to identify the neural correlates of these learning disorders in the context of arithmetic in more detail.

3.5 Conclusion

In this study, the effect of different presentation formats during arithmetic on brain activation was investigated in typically developing children. The results suggest that similar brain networks are involved in arithmetic with symbolic magnitudes, whereas clear differences between arithmetic with symbolic and non-symbolic formats were found. These differences might be explained by differences in the strategies children used to solve these arithmetic problems.

Appendix A

Table 1

Comparison of imaging and behavioral groups on age, arithmetic ability and reading ability

	Group	*M*	*SD*	Min.	Max.	*t*	df	*p*
Age	Imaging	10.74	0.87	9.28	12.12	1.82	57	.07
	Behavioral	10.36	0.70	8.99	11.49			
TTA	Imaging	4.55	3.10	1	10	1.25	57	.22
	Behavioral	3.59	2.64	1	10			
OMT	Imaging	8.00	3.02	1	14	-.81	57	.42
	Behavioral	8.65	2.93	2	15			

Table 2

Overview of behavioral results of the subtraction task

	Group	% Correct	*SD*	RT (ms)	*SD*
Dot arrays	Imaging	80.85	10.11	2453	516
	Behavioral	84.20	16.09	3264	297
Arabic digits	Imaging	97.82	3.34	1555	330
	Behavioral	96.83	7.14	1658	367
Number words	Imaging	95.74	3.82	1821	344
	Behavioral	96.00	4.92	2146	394

None of the participating children were diagnosed with learning disorders and none received remedial interventions.

We also analyzed the accuracy and reaction time scores of the subtraction task using a repeated measures ANOVA with format (dot arrays vs. Arabic digits vs. number words) as within-subject factor and group (imaging vs. behavioral) as between subjects factor. Regarding the accuracy scores, we found a main effect of format ($F(2,114) = 50.87$, $p < .001$), but no significant main effect of group ($F(1,57) = 0.30$, $p = .59$) and no interaction between format and group ($F(2,114) = 0.91$, $p = .40$). Turning to the reaction times, the main effects of format ($F(2,114) = 301.93$, $p < .001$) and group ($F(1,57) = 26.14$, $p < .001$) and the interaction between format and group ($F(2,114) = 24.01$, $p < .001$) were significant. In both groups, the response to subtraction items presented as digits were fastest, followed by words and dots (all p's $< .001$). Children who performed the subtraction task outside of the scanner were slower in responding than the children who did the task inside the scanner. Follow-up tests revealed that there were no group differences for digits ($t(57) = -1.08$, $p = .29$), but we did find group differences for number words ($t(57) = -3.21$, $p < .01$) and for dot arrays ($t(57) = -7.68$, $p < .001$).

Appendix B

Region, coordinates of the peak voxel, number of voxels (k) and t-value of activation clusters elicited by the contrasts [Digits – Fixation], [Words – Fixation] and [Dots – Fixation]. Only clusters consisting of more than 20 active voxels are mentioned.

Region	x	y	z	k	*t*
[Digits – Fixation]					
Right MOG & CB	28	-54	-24	1358	9.15
Left & Right MCC	-8	14	46	1014	11.19
Left SPL & IPL	-50	-38	56	788	8.30
Left IOG	-48	-78	-14	459	9.57
Right SPL	38	-48	56	136	7.64
Left Anterior Insula Lobe	-32	20	8	52	7.14
[Words – Fixation]					
Left & Right CB, Right IOG	36	-66	-24	4804	13.73
Left IOG, MOG & Fusiform Gyrus	-50	-72	-16	2462	11.38
Left Postcentral Gyrus, SPL & IPL	-32	-66	66	1876	9.54
Left & Right MCC	0	12	52	1795	10.83
Left MFG & Precentral Gyrus	-48	6	38	397	7.98
Left Anterior Insula Lobe	-28	32	8	150	7.74
Right IFG	48	8	24	145	8.47
Right Anterior Insula Lobe	34	24	4	144	9.15
Right IPL	38	-52	54	79	6.95
Right MFG	36	50	34	78	7.57
[Dots – Fixation]					
Left & Right SPL, IPL, IOG, MOG & CB	2	-72	-24	22664	19.73
Left & Right MCC & SFG	2	16	50	3741	14.99
Right Anterior Insula Lobe	36	20	6	1151	16.02
Right MFG	38	52	34	1029	11.18
Left Anterior Insula Lobe & Putamen	-30	22	8	1013	16.62
Right Precentral Gyrus	50	6	36	509	10.50
Left Precentral Gyrus	-52	6	40	277	8.75
Left MFG	-38	56	22	71	8.52

Note. MOG = middle occipital gyrus, CB = Cerebellum, MCC = middle cingulate cortex, SPL = superior parietal lobule, IPL = inferior parietal lobule, IOG = inferior occipital gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, SFG = superior frontal gyrus.

CHAPTER 4

Arithmetic in dyscalculia and dyslexia: Different behavioral, yet similar brain activity profiles

Abstract

Children with specific learning disorders (dyslexia, dyscalculia) often have problems with arithmetic. These difficulties are assumed to originate from brain abnormalities that remain unclear. Despite the high comorbidity between dyscalculia and dyslexia, this comorbidity has not been studied at the neural level. We used fMRI to investigate brain activity in children with dyslexia, dyscalculia, and comorbid dyslexia/dyscalculia.

Participants were 62 children aged 9 to 12. All children underwent fMRI scanning whilst performing an arithmetic task in different formats (dot arrays, digits and number words) and a reading task.

At the behavioral level, children performed as expected: children with dyscalculia performed poorly on all formats of the arithmetic task, whilst children with dyslexia only scored poorly on the digits and number words, and on the reading task. At the neural level, typically developing children showed higher brain activity during both tasks compared to children with learning disorders. Subject generalization analyses further showed that the neural activation patterns of children with dyslexia, dyscalculia and dyslexia/dyscalculia were indistinguishable by a trained classifier in both tasks. These data suggest that, despite obvious differences at the behavioral level, the neural profiles of children with different specific learning disorders may be more similar than initially thought.

4.1 Introduction

Specific learning disorders, such as difficulties in learning to read (dyslexia) or calculate (dyscalculia), which have a neurobiological origin, are very common, affecting between 5 and 15 percent of primary school children (Gaddes, 2013; Peterson & Pennington, 2015; Rapin, 2016). These *neuro*developmental disorders have been found to be associated with higher rates of high school dropout, higher levels of psychological distress, higher rates of unemployment and lower income in later life (American Psychiatric Association, 2013). Research has thus far mainly focused on differentiating the cognitive deficits associated with these specific learning disorders: deficits in phonological processing for dyslexia (Gabrieli, 2009; Ozernov-Palchik et al., 2016; Stanovich et al., 1994; Wagner & Torgesen, 1987) and deficits in number processing for dyscalculia (Ansari, 2008; Ashkenazi et al., 2013; Butterworth et al., 2011; Mazzocco et al., 2011; Rousselle & Noël, 2007). On the other hand, it turns out that difficulties in arithmetic, which are obviously the hallmark of dyscalculia, are also remarkably common in dyslexia, particularly when it comes to retrieving arithmetic facts from semantic memory, as is the case in multiplication (De Smedt & Boets, 2010; Göbel, 2015; Simmons & Singleton, 2008; Träff & Passolunghi, 2015). A possible explanation for this finding is that fact retrieval might be influenced by phonological processes (De Smedt et al., 2010; Dehaene et al., 2003), which are the key deficits in children with dyslexia.

In the DSM-5 (American Psychiatric Association, 2013), specific learning disorders are classified as *neuro*developmental disorders, as they are presumed to be biological in origin. However, the proportion of research dedicated to investigating the neurobiological origin of specific learning disorders is rather low, especially compared to other neurodevelopmental disorders similar in prevalence, such as ADHD and autism (Bishop, 2010). Developmental fMRI studies have demonstrated that arithmetic recruits a whole brain network in children (see Kaufmann et al. 2011 and Menon 2015 for reviews), and the limited amount of neuroimaging research in children with dyscalculia has so far shown mixed results of both hypo- and hyper-activation in this whole brain network in children with dyscalculia compared to their typically developing peers (Ashkenazi et al., 2012; Berteletti et al., 2014; Butterworth et al., 2011; Davis et al., 2009; De Smedt et al., 2011; Rosenberg-Lee et al., 2015). Turning to reading, it has been shown that a left-lateralized whole brain network is typically recruited (Houdé et al., 2010; Martin et al., 2015), and again research has reported both hypo- and hyper-activation in children with dyslexia compared to typically developing children (Gabrieli, 2009; Georgiewa et al., 2002; Hoeft et al., 2007; Richlan et al., 2009).

There are currently no studies available that directly investigated and compared the specificity of the neural correlates of dyslexia and dyscalculia. Furthermore, the prevalence of the combination of both, comorbid dyslexia/dyscalculia, is very high (around 40%; Wilson et al. 2015), yet to date there has been no neuroimaging research performed investigating the neurobiological origin of this comorbidity. Even more, this high comorbidity has been vastly overlooked in previous neuroimaging research in these disorders, as arithmetic ability is often not taken into account in dyslexia research, and children with low reading ability are typically discarded in dyscalculia research.

In this study, we therefore directly compared the neural correlates of dyslexia, dyscalculia and comorbid dyslexia/dyscalculia in subject groups comprising only children with strict formal diagnoses set by experienced clinicians. Children performed an arithmetic task inside the MRI scanner in which we manipulated presentation format (dot arrays, Arabic digits or number words). Compared to controls, we expected children with dyscalculia and children with comorbid dyslexia/dyscalculia to show behavioral and neural differences compared to typically developing children on all formats, given their general arithmetic problems. In contrast, children with dyslexia were expected to manifest differences only on symbolic formats, in particular number words, given their poor reading abilities. In addition to the arithmetic task, children also performed a reading task in the scanner. By definition, children with dyslexia and children with comorbid dyslexia/dyscalculia, but not children with only dyscalculia, were expected to perform more poorly on this task, and to show aberrant neural activation compared to their typically developing peers.

Three types of analyses were used to gain more insight into the differences and similarities in neurobiological origin of dyslexia and dyscalculia. First, we used whole brain univariate analyses to check for hypo- or hyper-activation in the groups under study. Second, we used multivariate subject classification analyses to investigate whether children with dyslexia or dyscalculia recruited similar neural networks compared to typically developing children. Finally, we used multivariate subject generalization analyses to directly and statistically test the dissimilarity and/or similarity of the recruited neural activation patterns of children with dyslexia, dyscalculia and comorbid dyslexia/dyscalculia.

4.2 Materials and Methods

4.2.1 Participants

Participants were 62 children (34 male) aged 9 to 12 years old (*M* = 10.83 years, *SD* = 0.83). All children with specific learning disorders included in the study (*n* = 39) received a formal diagnosis of a specific learning disorder by an experienced clinician in accordance with DSM-5 (American Psychiatric Association, 2013) standards. These children were further classified into three groups, depending on their diagnosis: children with dyslexia (DL, *n* = 19), children with dyscalculia (DC, *n* = 11), and children with comorbid dyslexia/dyscalculia (DLDC, *n* = 9). These groups of children with specific learning disorders were matched to a sample of typically developing children (TD, *n* = 23) without any history of learning difficulties. The data of these TD children were previously reported by Peters et al. (2016). Children were recruited from all over Flanders via schools, speech therapists, and online advertisement. None of the children had been diagnosed with additional developmental disorders, and none of them reported a history of any psychiatric or neurological illness. All children had normal or corrected-to-normal vision, their parents gave written consent, and they were paid for their participation. The study was approved by the Medical Ethical Committee of KU Leuven.

We further validated these clinical diagnoses by administering additional standardized tests for arithmetic and reading ability, as well as intelligence (see Table 4.1). Arithmetic ability was measured using the Tempo Test Arithmetic (TTA; de Vos 1992), a standardized timed paper-and-pencil task that consists of addition, subtraction, multiplication and division problems. The assessment of reading ability consisted of the standardized One Minute Test (OMT; Brus and Voeten 1979), in which children have to read aloud as many words correctly as possible within one minute, and the standardized Klepel (Van den Bos et al., 1994), a timed pseudo-word reading test which registers how many non-words a child can read aloud within two minutes. Intelligence was measured using the Vocabulary and Block Design subtests of the Dutch Wechsler Intelligence Scale for Children, Third Edition (WISC-III-NL; Kort et al. 2005). Analyses showed that the four groups were matched on age. Children with dyscalculia performed worse on the Tempo Test Arithmetic compared to children without dyscalculia, whilst children with dyslexia did not differ from typically developing children. Turning to reading ability, children with dyslexia scored weaker than children without dyslexia. All children scored within the normal range on the intelligence subtests, although children with dyscalculia performed significantly more poorly than children without dyscalculia on Block Design, a finding that has been observed in earlier studies (e.g., Kucian et al. 2011; Berteletti et al. 2014). On Vocabulary, children with comorbid dyslexia/dyscalculia scored lower than children from the other groups, but their scores were close to the population average, which indicated that their intellectual abilities were within the normal range.

Table 4.1

Means and standard deviations per group of the standardized assessment

Measure	TD		DL		DC		DLDC	
Age in years	10.71 $_a$	(0.86)	10.81 $_a$	(0.91)	11.06 $_a$	(0.88)	10.92 $_a$	(0.54)
Arithmetic ability $_{(1)}$	4.70 $_a$	(3.02)	3.32 $_{a, b}$	(2.34)	1.73 $_{b, c}$	(1.27)	1.22 $_c$	(0.44)
Reading ability $_{(2)}$	9.07 $_a$	(2.41)	4.08 $_b$	(2.51)	8.41 $_a$	(2.56)	4.11 $_b$	(1.71)
Block Design $_{(2)}$	13.13 $_a$	(2.60)	12.26 $_a$	(2.00)	8.55 $_b$	(2.02)	8.00 $_b$	(1.87)
Vocabulary $_{(2)}$	11.82 $_a$	(2.26)	11.95 $_a$	(3.10)	11.36 $_{a, b}$	(2.25)	9.22 $_b$	(2.33)

Note. TD = typically developing children, DL = children with dyslexia, DC = children with dyscalculia, DLDC = children with comorbid dyslexia/dyscalculia; (1) decile scores; (2) standardized scores: $M = 10$, $SD = 3$. For reading ability, the mean standardized score of the One Minute Test and the Klepel was used. For each variable under study, means that share the same index did not differ statistically on a $p < .05$ level.

4.2.2 Imaging study

4.2.2.1 Arithmetic task

The arithmetic task reported previously by Peters et al. (2016) was performed by the children in the scanner. In this task, children were asked to subtract numbers below 10 and to indicate whether the solution equaled a reference magnitude. This reference changed according to the run and was either 4 or 5 (presented in the fixed order of [4 5 4 5]). The format in which the numbers were presented varied, resulting in three format conditions: dot arrays, Arabic digits and number words. Subtraction exercises were presented in two halves of a white circle on a black background. Children were asked to subtract the number in the lower half of the circle from the number in the upper half (see Figure 4.1), and to respond using two response buttons on a response box. All stimuli were created using an adapted version of a Matlab script (Dehaene et al., 2005) and were controlled for parameters such as total area, item size (for the dot arrays) and amount of visual information (i.e., number of black pixels) by varying font size. The design of the task is illustrated in Figure 4.2

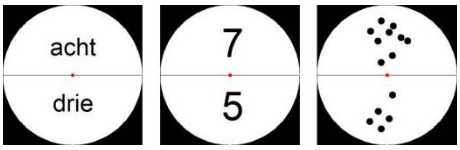

Figure 4.1. Examples of stimuli presented as number words, Arabic digits and dot arrays.

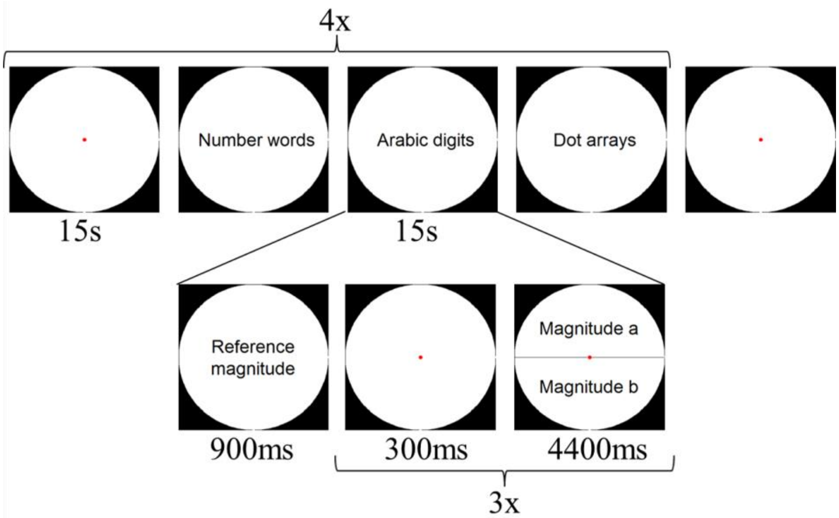

Figure 4.2. Schematic overview of the arithmetic task.

4.2.2.2 Reading task

Children also performed a reading task in the scanner, that was comparable to tasks used in previous fMRI studies on reading (e.g., Cao et al. 2006; Hoeft et al. 2006). The task was adapted to Dutch. Because Dutch, just like French, has a more transparent orthography compared to English, the design of this task was based on the paradigm used in Simon et al. (2005). Children were visually presented with existing Dutch words, and were instructed to indicate either whether the word included the phoneme /e:/ (phoneme condition), or whether a word was presented in upper or in lower case (visual condition). All words comprised the grapheme ‘e’, because in Dutch this grapheme has the most inconsistent grapheme-phoneme associations. For example, the grapheme ‘e’ can be read as /e:/ (as in ‘lego’ or ‘feest’ – *party*), as /i/ (as in ‘lied’ – *song*), as /ø/ (as in ‘neus’ – *nose*), as /ɛɪ/ (as in ‘reis’ – *journey*), as /u/ (as in ‘hoek’ – *corner*) or as /ə/ (as in ‘beton’ – *concrete*).

Fixation blocks and three task blocks were alternated and lasted 15 seconds each. A task block comprised a schematic instruction of the task at hand (1500ms), and four trials consisting of a short fixation (200ms) and the stimulus (3175ms). The schematic instruction consisted of a white face on a black background with an arrow pointed towards the ear for the phoneme condition (as children were instructed to check whether the grapheme ‘e’ *sounded like* /e:/), and with an arrow pointed towards the eye for the visual condition (as children had to *look* whether the letters were presented in upper case or in lower case). A run consisted of six blocks of both conditions (phoneme and visual) and lasted 255 seconds. Participants performed two runs. Words were presented in a white circle on a black background created by the Matlab script (Dehaene et al., 2005). Children were asked to press the left response button when an /e:/ sound was detected in the word (phoneme condition) or when the word was presented in upper case (visual condition), and to use the right response button when the ‘e’ was associated with another phoneme for the phoneme condition, and when a word was presented in lower case for the visual condition. The design of the task is illustrated in Figure 4.3.

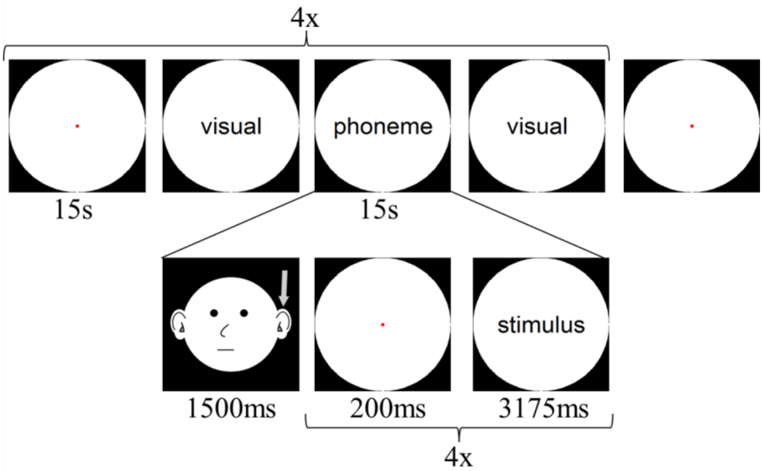

Figure 4.3. Schematic overview of the reading task.

4.2.2.3 Scanning parameters

Imaging data were collected via a 3T Philips Ingenia CX Scanner, at the Department of Radiology of the University Hospital in Leuven, with a 32-channel head coil and an EPI sequence (52 slices, 2.19 x 2.19 x 2.2 mm voxel size, interslice gap 0.3 mm, TR = 3000 ms, TE = 29.8 ms, flip angle = 90 degrees, 96 x 95 acquisition matrix). Furthermore, a high-resolution T1-weighted anatomical image (182 slices, resolution 0.98 x 0.98 x 1.2 mm, TE = 4.6 ms, 256 x 256 acquisition matrix) was acquired for each participant. Stimuli were displayed using PsychToolbox 3 (Brainard, 1997) and presented via an NEC projector onto a screen located approximately 46 cm from participants' eyes, which was visible via a mirror attached to the head coil.

4.2.3 Procedure

Data collection took place in two separate sessions. During the first session, the standardized behavioral assessment was carried out. Children were also intensively informed on the scanning procedure, and trained via a mock scanner in an environment that resembled the scanner environment as best as possible. The children practiced the arithmetic and the reading task in the mock scanner, whilst the noise of the scanner was simulated. During the second session, brain imaging data were collected at the University Hospital in Leuven. First, data were collected whilst children performed the arithmetic task. Second, the T1 anatomical image was acquired. Finally the functional data of the reading task were collected. Despite training with the mock scanner, three children (2 DL, 1 DLDC) were not comfortable enough in the scanning environment to successfully complete the scanning protocol.

4.2.4 Analyses

4.2.4.1 Behavioral analyses

Behavioral data were analyzed using SPSS (IBM SPSS Statistics 23; IBM Corp., Chicago, IL, USA). A Bonferroni correction was applied in all analyses to control for multiple comparisons. Trials in which participants did not respond, or responded too late due to the time limit (4400ms for arithmetic, 3175ms for reading) were discarded in the accuracy scores and reaction times.

4.2.4.2 fMRI preprocessing and analyses

For the analyses of the imaging data, the Statistical Parametric Mapping software package (SPM8, Wellcome Department of Cognitive Neurology, London) was used. To avoid a decrease in data quality due to excessive motion during scanning, all runs in which participants showed excessive movement (i.e., movement of more than one voxel size (2.2 mm) on two consecutive images) were removed from all analyses. Per task, subjects with less than half of the runs remaining were also discarded. For the arithmetic task, this criterion led to the discarding of seven additional participants (1 TD, 3 DL and 3 DC), leading to a final sample of 52 children (22 TD, 14 DL, 8 DC and 8 DLDC). In the reading task, which always came at the end of the scanning sequence, 14 participants were discarded due to excessive motion (2 TD, 6 DL, 4 DC and 2 DLDC), leading to a final sample of 45 children (21 TD, 11 DL, 7 DC and 6 DLDC). Of these remaining subjects, 10.33% of the runs of the arithmetic task, and 13.33% of the runs of the reading task were discarded in the analyses due to motion. The four groups of children did not differ in degree of motion in either of the tasks after this correction ($F(3,48) = 1.39$, $p = .26$ for the arithmetic task, $F(3,41) = 1.07$, $p = .37$ for the reading task).

Functional images were corrected for slice-timing differences, and for head motion artifacts by realigning all images to the first image. Functional images were co-registered to the anatomical image. Both functional and anatomical images were normalized to the standard Montreal Neurological 152-brain average template, and finally, functional images were smoothed using a Gaussian kernel of 10 mm full-width at half maximum (FWHM). The effect of the experimental conditions per voxel was estimated by creating a general linear model per participant. Motion realignment parameters were included as regressors of no interest in the general linear models, to further control for variation due to movement artifacts.

To statistically test which brain regions were activated more for one group of children compared to another, a whole brain, full factorial ANOVA with dyslexia and dyscalculia as between subject factors was performed on the imaging data, for each format versus fixation. A false discovery rate (FDR, $p < .05$) correction was applied to correct for multiple comparisons.

A subject classification analysis was further used to investigate whether we could classify children into their diagnostic group based on their neural activation patterns for each format versus fixation. Unlike in the full factorial ANOVA, this analysis does not use a voxel-to-voxel activity based comparison, but rather compares spatial patterns of activation in selected regions of interest (ROIs). As arithmetic and reading recruit a large, whole brain network, five large ROIs were selected with anatomical masks from the WFU PickAtlas: whole brain grey matter, occipital lobe, parietal lobe, frontal lobe and temporal lobe. A leave-pair-out-cross-validation (LPOCV) was used (Ung et al., 2014), in which the classifier was trained on the participants of two groups, except one randomly selected pair of subjects (one from each group). The classifier was then tested on the remaining pair of subjects. This procedure was repeated until each participant was left out of training once. This LPOCV-procedure was run 1000 times. Classification accuracies were then averaged over these repetitions. As our group sizes differed over groups, the smallest group size was used. Participants from the larger group were randomly left out of the LPOCV-iteration to match the group size of the smaller group. To determine the critical classification value, a Monte Carlo Permutation test was performed (Mourão-Miranda, Bokde, Born, Hampel, & Stetter, 2005). In this test, category labels of the training set were randomly permuted, followed by 1000 iterations of the LPOCV-procedure. Subsequently, the significance border was set using the 95% confidence interval cutoff on these 1000 iterations. This analysis was performed for both tasks, and was run twice per ROI: once to differentiate TD from DL+ (DL + DLDC), and once to differentiate TD from DC+ (DC + DLDC).

We also applied a subject generalization analysis to investigate whether the activation patterns of groups of children with learning disorders were interchangeable or not. The LPOCV-procedure from the subject classification analysis was used, with the exception that in this analysis, the model was trained on differentiating TD children from one learning disorder group (e.g., DL), and tested on differentiating TD children from another learning disorder group (e.g., DC). Generalizing over two groups always occurred bidirectional: The model was trained on DL and tested on DC, but in addition also trained on DC and tested on DL. This generalization is only significant if neural activation patterns of the DL and DC groups are very similar, fooling the model into thinking the activation patterns belong to the same group. Again, a Monte Carlo Permutation test was performed to determine the significance cutoff criterion. This analysis was performed for both the arithmetic and the reading tasks, and was run three times per ROI: once to generalize between DL and DC, once to generalize between DL and DLDC, and once to generalize between DC and DLDC.

4.3 Results

4.3.1 Behavioral results

4.3.1.1 Arithmetic task

To look into the behavioral results of the arithmetic task (see Figure 4.4), mixed ANOVAs with the presence of dyscalculia and the presence of dyslexia as between-subject factors, and format (dots vs. digits vs. words) as within-subject factor were performed on accuracies, reaction times and percentages of non-response. Details on main and interaction effects per analysis are presented in supplementary section 1 and in Supplementary Table 1.

In summary, differences and similarities were found between children with different learning disorders. At the one hand, children with dyscalculia and with comorbid dyslexia/dyscalculia were less accurate and more often late in responding compared to children with dyslexia and typically developing children, especially on the dots. On the other hand, all children with learning disorders were slower in responding compared to typically developing children.

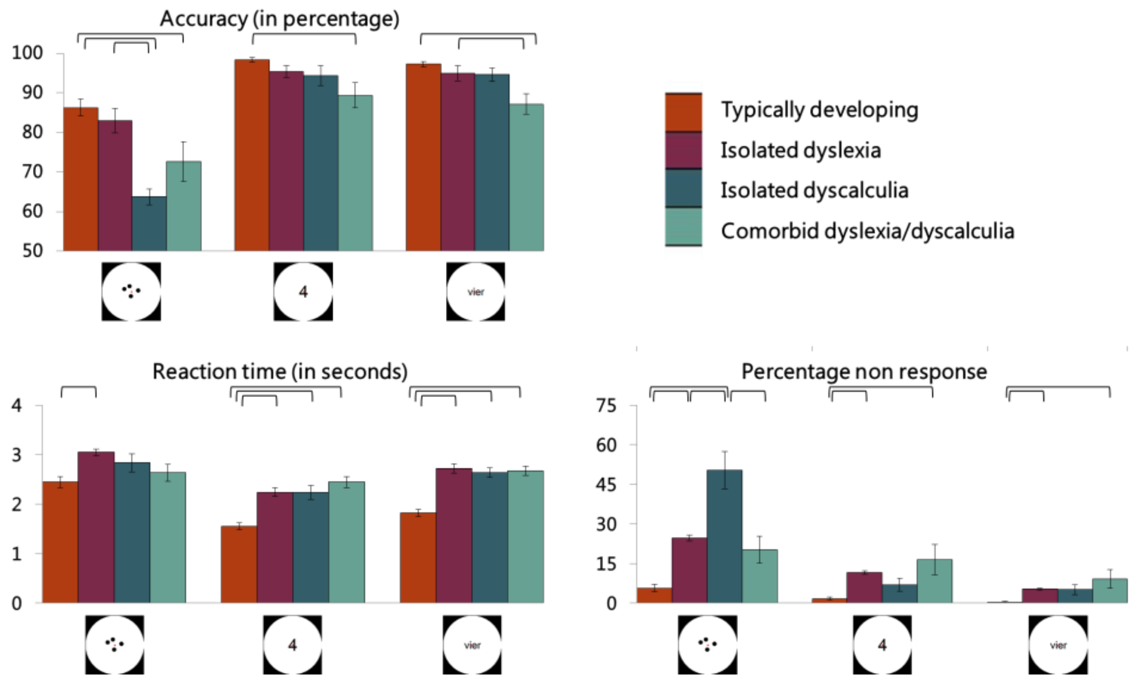

Figure 4.4. Mean accuracy, reaction time (in seconds) and percentage non-response on the arithmetic task per format (dots, digits and words) and per group. Error bars represent the standard error of the mean. Means connected by brackets differ significantly on a p < .05 level.

4.3.1.2 Reading task

Three-way ANOVAs with the presence of dyscalculia and the presence of dyslexia as between-subject factors, and condition (phoneme vs. visual) as within-subject factor were performed on the accuracy scores, the reaction times and the percentages non-response (see Figure 4.5). Details on main and interaction effects per analysis are shown in supplementary section 2 and in Supplementary Table 2.

In summary, results showed that children with dyslexia were less accurate and more often late in responding compared to typically developing children. As was the case in the arithmetic task, typically developing children also reacted faster than children with dyslexia, dyscalculia and comorbid dyslexia/dyscalculia.

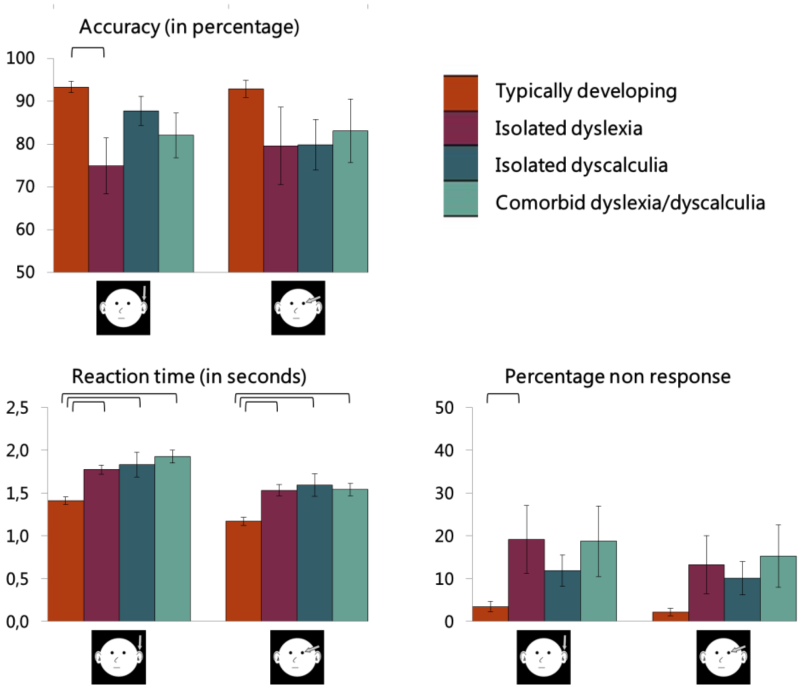

Figure 4.5. Mean accuracy, reaction time (in seconds) and percentage non-response on the reading task per condition (phoneme on left, visual on right) per group. Error bars represent the standard error of the mean. Means connected by brackets differ significantly on a $p < .05$ level.

4.3.2 Imaging results

4.3.2.1 Arithmetic task

4.3.2.1.1 Differences between children with learning disorders and controls

Whole brain, full factorial ANOVAs with dyslexia and dyscalculia as between-subject factors were performed on all formats versus fixation (see Figure 4.6). These analyses showed that typically developing children elicited more activation for dot arrays compared to children with dyscalculia and children with dyslexia, and these effects were spread out over a whole brain network, in frontal, parietal, temporal and occipital regions. For the Arabic digits, we also found higher activation levels for typically developing children compared to children with dyslexia in a smaller set of regions, which included the left posterior and inferior parietal areas, bilateral cuneus, left middle temporal gyrus and left inferior frontal gyrus. The comparison of typically developing children with children with dyscalculia showed a similar pattern of results at the uncorrected level ($p < .001$), but this pattern did not survive FDR correction. Similar results were found for the number words: Typically developing children showed higher activation levels compared to children with dyslexia in left posterior and inferior parietal areas, bilateral cuneus and inferior and middle occipital areas, bilateral middle temporal gyrus and bilateral inferior frontal gyrus. This pattern of findings was also present for typically developing children versus children with dyscalculia, albeit at an uncorrected level ($p < .001$). Over all formats, there were no brain regions that were activated more in children with a learning disorder compared to typically developing children, also not on an uncorrected level ($p < .001$). Likewise, direct comparisons of children with learning disorders revealed no brain regions activated more in children from one group compared to another, also not on an uncorrected level ($p < .001$).

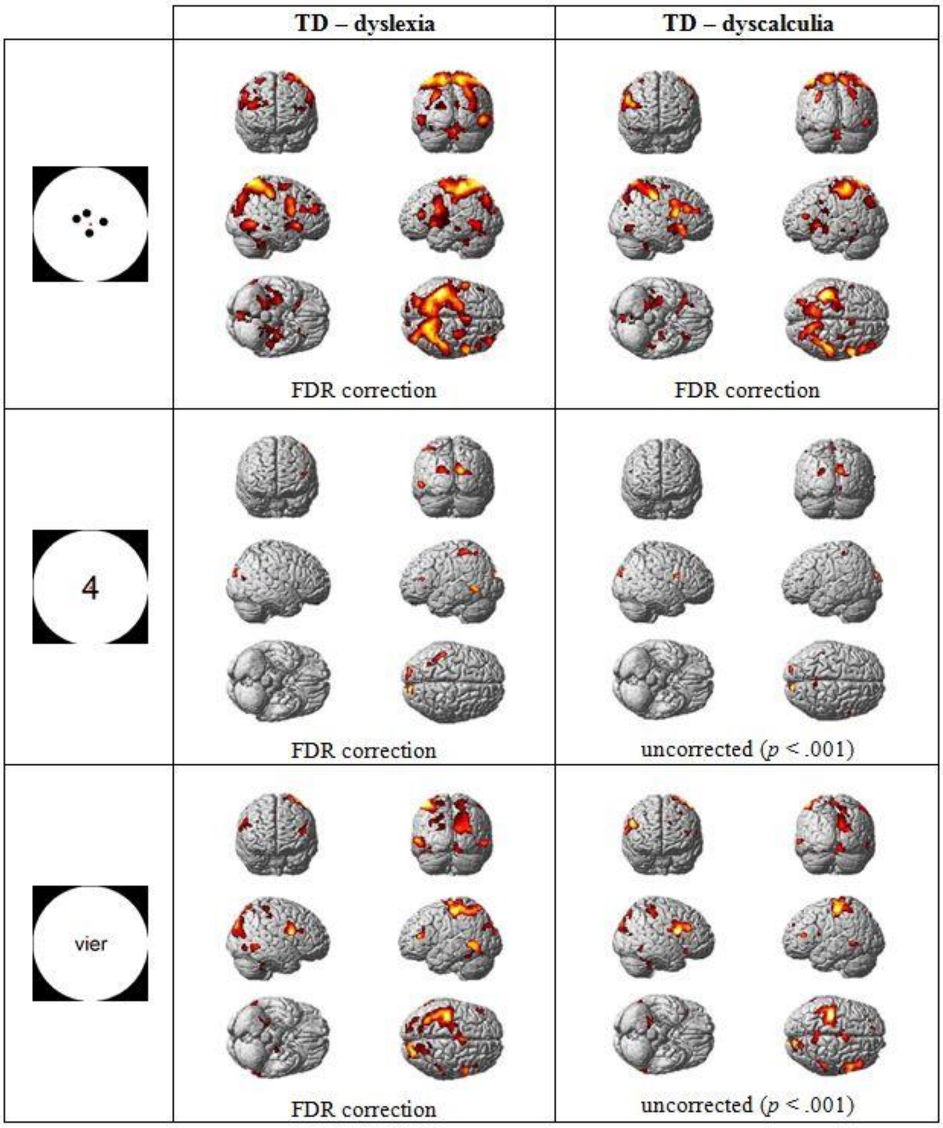

Figure 4.6. Activation patterns of all three formats (dot arrays, Arabic digits and number words) of the arithmetic task versus fixation, of typically developing children versus children with dyslexia (on the left) and typically developing children versus children with dyscalculia (on the right). Activation patterns are shown uncorrected only if no activation clusters survived FDR-correction.

As an additional statistical test of differences between subject groups, we performed multi-voxel subject classification analyses. These analyses (see Figure 4.7) allowed us to investigate whether we could classify children into their group (typically developing, dyslexia, or dyscalculia) based on their neural activation *pattern* during arithmetic and this was done for each format.

The classification analysis differentiating typically developing children from children with dyslexia showed that for dots, digits and words, and in each ROI (whole brain, occipital lobe, parietal lobe, frontal lobe and temporal lobe) we were able to significantly differentiate typically developing children from children with dyslexia based on their neural activation pattern. The only region in which the classification during Arabic digits did *not* reach significance, was the temporal lobe. In other words, in temporal lobe, the neural activation patterns elicited by Arabic digits were thus insufficiently distinct between typically developing children and children with dyslexia. In all other regions however, the neural activation patterns elicited by all formats of our task allowed a trained model to accurately categorize children into typically developing children and children with dyslexia.
For the differentiation between typically developing children and children with dyscalculia, a similar pattern of findings was found in parietal and frontal lobes: Classification was significantly accurate for dots, digits and words. At the whole brain level, classification was significant for dots and words, in the occipital lobe for words only, yet in the temporal lobe classification did not reach significance for any of the formats. Our trained classifier was thus able to correctly categorize typically developing children and children with dyscalculia based on the neural activation patterns elicited by all formats in frontal and parietal areas. All findings above suggest that children with learning disorders showed distinct neural activation patterns compared to typically developing children.

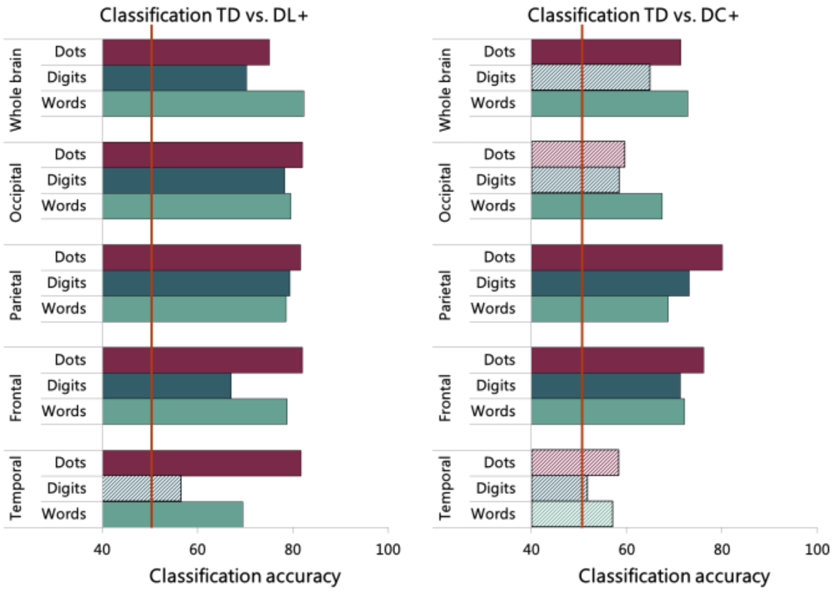

Figure 4.7. Classification accuracies per format (dots, digits and words) and per ROI (whole brain, occipital, parietal, frontal and temporal lobes) for the arithmetic task. Accuracies that reached significance are solidly filled, and chance level (0.50) is indicated.

4.3.2.1.2 Similarities between children with different learning disorders

Visual inspection of the whole-brain univariate analyses in the previous section suggested that the regions activated more by typically developing children than by children with dyscalculia and by children with dyslexia were anatomically similar: The regions that were more activated in typically developing children compared to children with dyslexia tended to be the same as the regions activated more by typically developing children compared to children with dyscalculia. Furthermore, results from the subject classification analyses indicated that the neural activation patterns of typically developing children were distinct from the neural activation patterns of children with dyslexia and of children with dyscalculia.

Because there was only a small number of subjects in each of the groups with learning disorders, the direct univariate comparisons of the activation patterns of the different groups were underpowered, in particular because similarity in activation differences would amount to a null result: no differences between learning disorders. Furthermore, even *if* univariate between-group differences were found with this relatively small subject sample, these direct contrasts would not show the magnitude of these differences relative to the similarities between learning disorders and potentially observed differences could be very small relative to the existing similarities. To answer these questions and to statistically test the degree of similarity suggested by visual inspection in Figure 4.6, we performed multi-voxel subject generalization analyses in which we tested the ability of the trained multi-voxel classifiers to generalize from one learning disorder to the other.

These multi-voxel subject generalization analyses showed that a classifier that was trained to distinguish between typically developing children and a second group of children with one learning disorder (e.g., dyslexia) and tested on differentiating typically developing children from a group of children with a different learning disorder (e.g., dyscalculia) was significantly accurate for all formats and in all regions, except for digits in temporal cortex (see Figure 4.8). Thus, overall, the atypical activation patterns observed in dyslexia generalize significantly to the atypical activation patterns observed in dyscalculia, and vice versa. Maybe less surprisingly, the generalization also works from groups with a single isolated learning disorder to the comorbid group. These results clearly show that the neural activation patterns of all formats during this task of children with learning disorders (dyslexia, dyscalculia or comorbid dyslexia/dyscalculia) were sufficiently similar to be mistaken for activation patterns from children of a different learning disorder group. This indicates that the neural activation patterns were similar across learning disorders but in turn distinct from the neural activation patterns of typically developing children.

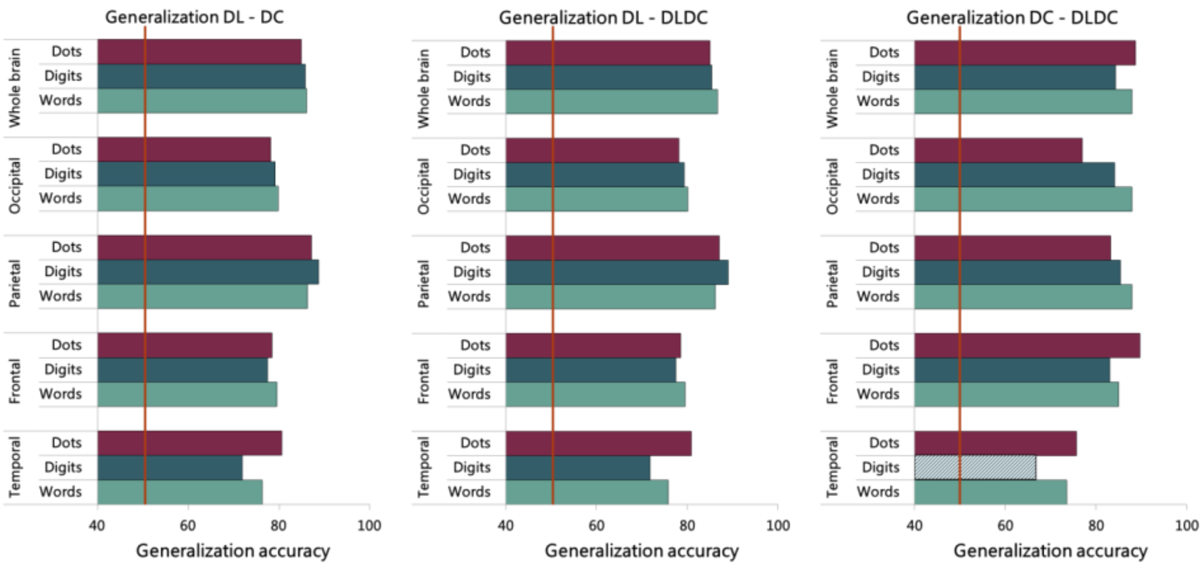

Figure 4.8. Generalization accuracies per format (dots, digits and words) and per ROI (whole brain, occipital, parietal, frontal and temporal lobes) for the arithmetic task. Accuracies that reached significance are solidly filled, and chance level (0.50) is indicated.

4.3.2.2 Reading

4.3.2.2.1 Differences between children with learning disorders and controls

The whole brain, full factorial ANOVA performed on the two conditions of the reading task (phoneme and visual) showed no regions that were more active for one group of children compared to another. At the uncorrected level (*p* < .001), typically developing children elicited more activation compared to children with dyslexia and dyscalculia in left superior parietal areas, left supramarginal gyrus, right cuneus, left superior temporal gyrus, and left medial frontal gyrus. for the phoneme condition, and in left postcentral gyrus for the visual condition. Furthermore, the differences in activation were anatomically similar for typically developing children vs. children with dyslexia compared to typically developing children vs. children with dyscalculia for both conditions (see Figure 4.9). Over both conditions, there were no brain regions that were recruited more by children with a learning disorder compared to typically developing children, also not on an uncorrected level (*p* < .001).

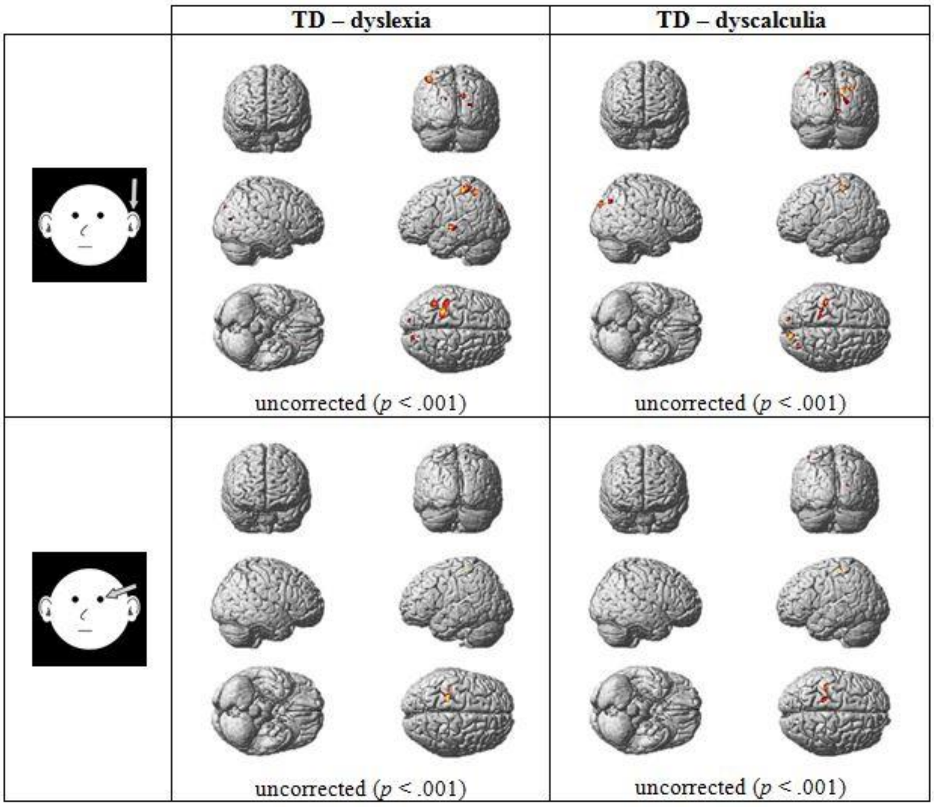

Figure 4.9. Activation patterns of both conditions (phoneme and visual) of the reading task versus fixation of typically developing children versus children with dyslexia (on the left) and versus children with dyscalculia (on the right). Activation patterns are shown uncorrected, because no activation clusters survived FDR correction.

Likewise, direct comparisons of children with learning disorders revealed no brain regions activated more by children from one group compared to another, also not on an uncorrected level ($p < .001$). Note that these analyses might lack power due to the lower number of participants in this second experiment.

Subject classification analyses (see Figure 4.10) were performed to look into the (dis)similarity of neural activation patterns between groups. Classifying children as typically developing vs. dyslexic was possible for both conditions on a whole brain level and in the frontal lobe. In the parietal lobe, only the activation patterns elicited by the phoneme condition allowed us to classify children with significant accuracies. In temporal and occipital lobe, classification accuracies did not reach significance for either of the conditions. Classifying children as typically developing vs. dyscalculic on the other hand was possible for both conditions in the parietal lobe, and for the phoneme condition in occipital lobe. In the other ROIs, classification did not reach significance. These results point towards different neural networks recruited for typically developing children compared to children with dyslexia or dyscalculia, although we cannot exclude the possibility that some of the apparent differences are related to a threshold effect and a low number of participants. We lack the power, for example, to prove that the nonsignificant classification of TD vs DC+ in the whole-brain ROI is significantly different from the significant classification of TD vs DL+ in that same ROI. This problem is overcome by the generalization analysis.

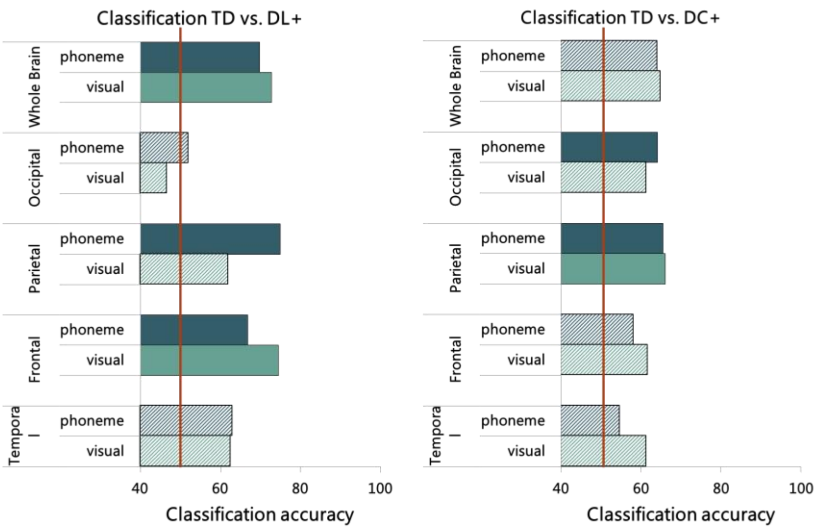

Figure 4.10. Classification accuracies per task (phoneme and visual) and per ROI (whole brain, occipital, parietal, frontal and temporal lobes) for the reading task. Accuracies that reached significance are solidly filled, and chance level (0.50) is indicated.

4.3.2.2.2 Similarities between children with different learning disorders

Also in the reading task, visual inspection showed that similar neural regions were hypo-activated in children with dyslexia and dyscalculia compared to typically developing children (see Figure 4.9), although care must be taken to interpret these activation maps plotted at an uncorrected threshold. The data in the classification analyses revealed that it was not always the same ROI and the same task condition which showed a significant effect, but again this finding is difficult to interpret given that many results were just below or above the statistical threshold. Furthermore, as argued above, such differences can only be meaningfully interpreted if pitted against the degree of similarity between the learning disorders under study. We therefore performed the same multi-voxel subject generalization analyses as in 4.3.1.2.2 on the reading task to investigate whether the neural activation patterns of children with learning disorders were interchangeable, and hence very similar (see Figure 4.11).

Activation patterns for children with dyslexia only and children with dyscalculia only were interchangeable for both conditions at a whole brain level, and in parietal and frontal lobes. In the temporal lobe, generalization was only possible for the activation patterns elicited by the phoneme condition. In the occipital lobe, activation patterns were not similar enough to enable generalization. Activation patterns for children with dyslexia and children with comorbid dyslexia/dyscalculia were sufficiently similar to allow significant generalization at a whole brain level and in parietal and frontal lobes, for both conditions. In the occipital and temporal lobes, generalization was not possible for either condition. Finally, activation patterns of children with dyscalculia and children with comorbid dyslexia/dyscalculia allowed significant generalization for both conditions in the parietal lobe and at a whole brain level, for the phoneme condition in the occipital lobe, and for the visual condition in the frontal lobe. In the temporal lobe, generalization between children with dyscalculia and children with comorbid dyslexia/dyscalculia did not reach significance.

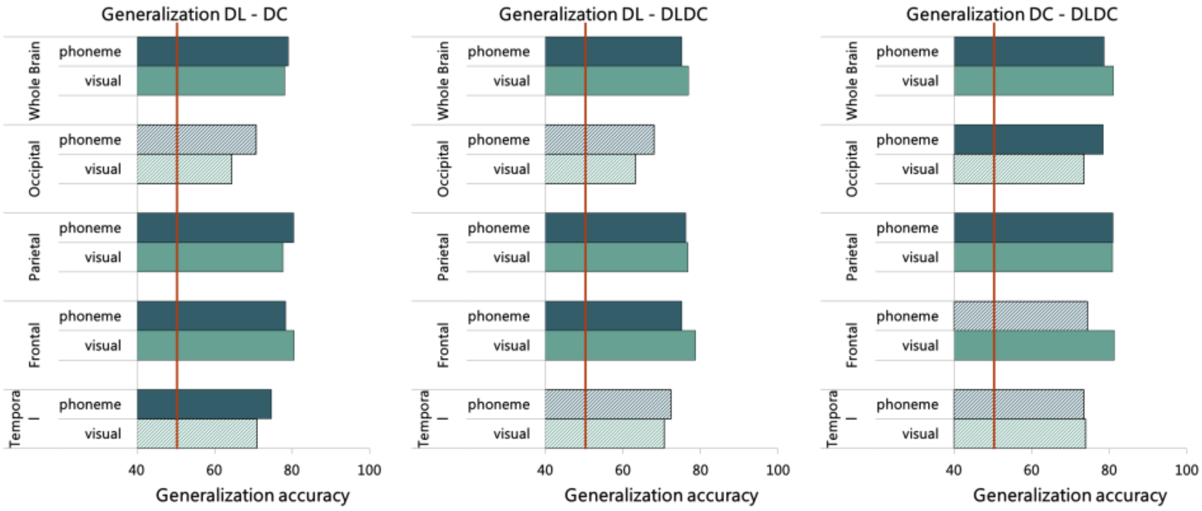

Figure 4.11. Generalization accuracies per task (phoneme and visual) and per ROI (whole brain, occipital, parietal, frontal and temporal lobes) for the reading task. Accuracies that reached significance are solidly filled, and chance level (0.50) is indicated.

4.4 Discussion

The current study investigated the neurobiological underpinnings of arithmetic and reading in children with dyslexia, children with dyscalculia, children with comorbid dyslexia/dyscalculia, and age-matched, typically developing children. Participants performed an arithmetic and a reading task whilst functional imaging data were acquired. This was the very first study in which the neural networks associated with arithmetic and reading were compared between these four groups of children with neurodevelopmental disorders.

In general, the behavioral findings were in line with what was hypothesized a priori: children with dyscalculia performed more poorly on all formats of the arithmetic task, yet most prominently on dot arrays, and children with dyslexia performed poorly on the symbolic formats (i.e., digits and number words; see e.g., Träff and Passolunghi 2015), and on the reading task. Children with comorbid dyslexia/dyscalculia performed similarly compared to children with dyscalculia on the arithmetic task, and similarly compared to children with dyslexia on the reading task, which could also be expected based on the literature (see e.g., Moll et al. 2015). In addition to these disorder-specific patterns, there were also some commonalities shared by the different learning disorders. In particular, all children with learning disorders were slower in responding in both tasks compared to typically developing children.

At the neural level, our findings point to a surprising degree of overlap between the different learning disorders. We observed hypo-activation for all children with learning disorders compared to typically developing children in the arithmetic task. These data are in line with earlier studies in dyscalculia. For example, Berteletti et al. (2014) observed hypo-activation in left inferior frontal gyrus, left temporal regions and right superior parietal lobule during small and large multiplications in children with dyscalculia compared to typically developing children. Similarly, Ashkenazi et al. (2012) reported hypo-activation in posterior and inferior parietal regions and in dorsolateral prefrontal cortex for small and large additions. On the other hand, our data are not in line with Rosenberg-Lee et al. (2015), in which hyper-activation was reported for children with dyscalculia compared to healthy controls in parietal, occipitotemporal and prefrontal regions for addition and subtraction problems (see also Davis et al. 2009). None of the previous imaging studies used validated, clinical diagnoses to categorize children into groups, and paradigms used in the various studies differed vastly. These differences in participants and methodology could possibly account for the discrepancies in results between the current study and previous studies.
Arithmetic difficulties, particularly with fact retrieval, are also very common in children with dyslexia (Göbel, 2015; Simmons & Singleton, 2008; Träff & Passolunghi, 2015). Thus far the only neuroimaging study investigating arithmetic in children with dyslexia (Evans et al., 2014), reported hypo-activation in left supramarginal gyrus in children with dyslexia compared to typically developing children during addition and subtraction. These results are in line with the hypo-activation found for children with dyslexia during arithmetic in the current study.

Turning to the reading task, we found very similar results compared to the results of the arithmetic task: children with dyslexia and children with dyscalculia showed hypo-activation compared to typically developing children. This hypo-activation in children with dyslexia is in agreement with previous research on dyslexia (Temple et al. 2001, 2003; see Gabrieli 2009 for a review; Ozernov-Palchik et al. 2016).

The current study is the first neuroimaging study that included children with dyslexia, children with dyscalculia and children with comorbid dyslexia/dyscalculia. In addition, we avoided missing comorbidity, which is a frequent problem in studies which only focus upon one of the two disorders. Therefore, we were able, for the first time, to directly compare the neural profiles of these groups of children which are very different in their everyday problems. The whole brain univariate analyses did not reveal any regions recruited more by one group of children with learning disorders than by another group. The absence of group differences between children with dyslexia and children with dyscalculia in terms of activation levels could however potentially reflect a power issue due to the rather small sample sizes. Therefore, we also performed multi-voxel subject classification and generalization analyses to investigate (dis)similarities in recruited neural activation patterns over groups. The subject classification analyses showed that the neural activation patterns of typically developing children were sufficiently distinct from the neural activation patterns of children with dyslexia and of children with dyscalculia for a trained model to classify children with dyslexia and children with dyscalculia and typically developing children correctly. This subject classification was very convincing in the arithmetic task and at least partially present in the reading task. The subject generalization analyses showed that, now very clearly in both tasks, the neural activation patterns of children with different learning disorders (dyslexia, dyscalculia and comorbid dyslexia/dyscalculia) were sufficiently similar to allow a trained classifier to generalize from one learning disorder to the other. It is furthermore remarkable that the generalization classification accuracies were not lower than the within-group subject classification accuracies. This further suggests that the individuals from the different learning disorder groups are very similar in how they differ from typically developing children in terms of brain activity. It is also important to note that these results are *by no means* null-results potentially caused by power issues, but significant, statistical tests of similarity between groups of children with different learning disorders.

It is useful to stress that part of the subject generalization analyses were done specifically on the groups with an isolated disorder (i.e., dyslexia and dyscalculia), excluding the comorbid group. Thus, it is impossible that the significant and robust classification accuracies were driven by the inclusion of children with comorbid dyslexia/dyscalculia in both groups (dyslexia and dyscalculia). In addition, generalization was also possible from the isolated dyslexia or dyscalculia group to the comorbid dyslexia/dyscalculia group. These results show that, at a neural level, children with comorbid dyslexia/dyscalculia vastly resemble both children with dyslexia-only and children with dyscalculia-only.

What might account for these unexpected neural similarities across the three neurodevelopmental learning disorders under study?

First of all, the observed findings could reflect a task difficulty effect. As the analyses on the reaction time data revealed, all children with learning disorders were slower in responding compared to typically developing children in both tasks, which could reflect an overall higher task difficulty level experienced by all children with learning disorders. Furthermore, in the most demanding format condition of the arithmetic task (dot arrays), the difference in activation levels between typically developing children and children with dyslexia and children with dyscalculia is more prominent in comparison to the less demanding format conditions (Arabic digits and number words). These results suggest that as task difficulty increases, children with learning disorders are less efficient in modulating neural activation in recruited neural networks. Future studies would benefit from using event-related designs which would allow to discard incorrect trials, and trials on which the participant did not respond (in time).

Second, these results could reflect differences in the recruitment of domain-general resources, such as working memory. Research has shown that working memory is affected in both dyscalculia (Swanson & Beebe-Frankenberger, 2004) and dyslexia (Smith-Spark & Fisk, 2007). As we found similar results in both tasks, it is possible that task-independent correlates such as working memory rather than task-specific correlates influenced our findings.

Third, this pattern of findings could also be explained by the characteristics of the tasks we designed, which were both academic as they tapped into arithmetic and reading. Previous research has shown that reading and arithmetic skills are correlated, likely due to the importance of reading skills in acquiring arithmetic knowledge (Fuchs et al., 2005, 2006; Hecht, Torgesen, Wagner, & Rashotte, 2001; Jordan, Hanich, & Kaplan, 2003). A study in monozygotic and dizygotic twins, has provided evidence in favor of the so called *generalist genes* hypothesis, which states that most genes associated with one academic skill (e.g., reading) will also be associated with another academic skill (e.g., arithmetic), be it that some genes will have more specific effects (Haworth et al., 2009). Furthermore, a study by Docherty et al. (2010) found SNPs associated with both arithmetic and reading ability. These similar genetic influences are thus presumed to lie at the base of the development of (problems with) both reading and arithmetic (Krapohl et al., 2014; Light & DeFries, 1995; Mascheretti et al., 2014; Plomin & Kovas, 2005). This genetic influence could thus affect the neurobiological origin of dyslexia, dyscalculia and comorbid dyslexia/dyscalculia in a similar way, which could result in aberrant neural modulation during academic tasks such as arithmetic and reading.

Finally, the degree of similarity between dyslexia, dyscalculia and comorbid dyslexia/dyscalculia is also somewhat reflected in the DSM-5, as it only speaks of specifiers of specific learning disorders with the same cognitive characteristics: difficulties in learning and using academic skills (American Psychiatric Association, 2013). The DSM-5's approach is more clinically oriented, and is likely based on the high comorbidity of problems in arithmetic and reading in clinical settings. Additionally, the use of specifiers rather than isolated learning disorders allows for variation in manifested deficits with development.

No matter how these four factors work (together) to result in highly overlapping atypical patterns of neural activation in the two learning disorders, fact remains that this overlap is highly unexpected given the literature which is dominated by studies focusing upon single disorders. Note that our two experiments are very representative for the experiments that researchers would design to study either dyscalculia (arithmetic task) or dyslexia (reading task). In a typical isolated study on an isolated disorder, researchers would be tempted to consider their findings as specific to the targeted disorder. Our study shows that this tunnel vision is unwarranted. This is even more so because many studies in the literature would ignore comorbidity, and thus include a less specific clinical group compared to our study.

Although we believe that our findings are extremely important as a benchmark to reconsider the dominant approach in the literature, much more work remains to be done. We do not exclude the possibility that, in addition to a shared atypical activation profile, there are also specific differences between dyslexia and dyscalculia that could be robustly found with very specific paradigms. Furthermore, other neural markers might provide a different result. In particular, it would be interesting to also look into (dis)similarities in neural connectivity between children with dyslexia, children with dyscalculia and children with comorbid dyslexia/dyscalculia. Previous research has reported hyper-connectivity between frontal and parietal areas in children with dyscalculia (Jolles et al., 2016; Rosenberg-Lee et al., 2015) and hypo-connectivity in children with dyslexia (see Vandermosten et al. 2012 for a review), but a direct comparison of connectivity between children with learning disorders has never been made.

Supplementary Materials

1. Behavioral results of the arithmetic task

Regarding the accuracy scores, a main effect of format was found ($F(2,96) = 106.23$, $p < .001$). Children performed worse on dot arrays than on Arabic digits and number words (both ps < .001), whereas the performance on digits and words did not differ ($p = .47$). Also, children with dyscalculia performed worse than children without dyscalculia ($F(1,48) = 27.65$, $p < .001$). On the other hand, children with and without dyslexia performed equally well ($F(1,48) = 1.39$, $p = .24$). There was a significant interaction between format and dyscalculia ($F(2,96) = 11.06$, $p < .001$), which can be explained by the larger difference between dyscalculic and non-dyscalculic children in performance on dots than on digits and words. The interaction effect between format and dyslexia ($F(2,96) = 4.48$, $p = .014$) on the other hand can be explained by the larger difference in performance on digits and words than on dots between dyslexic and non-dyslexic children. Finally, the interaction effect between dyslexia and dyscalculia was not significant ($F(1,48) = 0.25$, $p = .62$), indicating that reading ability did not influence the finding that dyscalculic children performed worse than children without dyscalculia.

Turning to the reaction times, we found a main effect of format ($F(2,96) = 43.32$, $p < .001$): children responded faster to digits than to words ($p < .001$), and faster to words than to dots ($p = .002$). Furthermore, non-dyscalculic children responded faster than children with dyscalculia ($F(1,48) = 9.50$, $p = .003$). Similarly, children without dyslexia responded faster than children with dyslexia ($F(1,48) = 19.38$, $p < .001$). Finally, the significant interaction effect between dyslexia and dyscalculia ($F(1,48) = 16.61$, $p < .001$) shows that typically developing children were faster than children with dyslexia, dyscalculia and comorbid dyslexia/dyscalculia.

As the task children performed in the scanner was a timed task, we also looked into the percentage of items that subjects were not able to solve within the given time limit. A significant main effect of format was present ($F(2,96) = 51.31$, $p < .001$). Subjects responded to fewer dot items than digit items ($p < .001$), and to fewer digit items than number words items ($p = .004$). Furthermore, children with dyscalculia responded to fewer items than children without dyscalculia ($F(1,48) = 18.98$, $p < .001$), whereas children with dyslexia responded to an equal number of items compared to non-dyslexic children ($F(1,48) = 1.74$, $p = .19$). Significant interaction effects between format and dyscalculia ($F(2,96) = 9.15$, *p* < .001) and format and dyslexia (*F*(2,96) = 6.80, *p* = .002) however, showed that the difference in non-response on dots was larger in dyscalculic children compared to non-dyscalculic children, whereas the difference in non-response on digits was larger in dyslexic children compared to non-dyslexic children. Finally, the interaction effect between dyslexia and dyscalculia (*F*(1,48) = 13.88, *p* < .001) reflected the fact that children with isolated dyscalculia solved the fewest items, and typically developing children the most.

Supplementary Table 1

Main effects and interaction effects of the arithmetic task

		Accuracy		Reaction time		Non response	
	df	*F*	*p*	*F*	*p*	*F*	*p*
Format	2,96	106.23	< .001	43.32	< .001	51.31	< .001
DL	1,48	1.39	.244	19.38	< .001	1.74	.194
DC	1,48	11.06	< .001	9.50	.003	18.98	< .001
Format x DL	2,96	4.48	.014	2.45	.091	6.80	.002
Format x DC	2,96	11.06	< .001	6.92	.002	9.15	< .001
DL x DC	1,48	0.25	.619	16.61	< .001	13.88	< .001
Format x DL x DC	2,96	5.51	.005	1.14	.323	22.04	< .001

<u>*2. Behavioral results of the reading task*</u>

For the accuracy scores, there was no effect of condition (*F*(1,41) = .056, *p* = .82), nor of dyscalculia (*F*(1,41) = .21, *p* = .65). The main effect of dyslexia was marginally significant (*F*(1,41) = 3.82, *p* = .058), indicating a trend towards a lower performance for dyslexic children compared to non-dyslexic children. The interaction effect between dyslexia and dyscalculia was not significant (*F*(1,41) = 2.81, *p* = .10), indicating that arithmetic ability did not influence the fact that dyslexic children seemed to perform slightly worse than non-dyslexic children. None of the other interaction effects reached significance (all *p*s > .25).

The analysis of the reaction times showed a main effect of condition (*F*(1,41) = 68.72, *p* < .001), with faster reaction times for the visual compared to the phoneme condition. Furthermore, both the main effect of dyslexia (*F*(1,41) = 7.31, *p* = .01) and dyscalculia (*F*(1,41) = 12.35, *p* = .001) were significant, indicating that children with dyslexia and with dyscalculia responded slower than non-dyslexic and non-dyscalculic children, respectively. The interaction effect between dyslexia and dyscalculia (*F*(1,41) = 5.69, *p* = .022) reflected the fact that typically developing children responded faster than dyslexic, dyscalculic and comorbid children. None of the other effects reached significance (all *p*s > .26).

Finally, the analysis of the percentage non-response revealed a main effect of condition ($F(1,41) = 7.15$, $p = .011$) and of dyslexia ($F(1,41) = 4.10$, $p = .05$). Fewer responses were given in the phoneme condition than in the visual condition, and dyslexic children were more often late in responding than non-dyslexic children. The interaction effect between dyslexia and dyscalculia was not significant ($F(1,41) = 0.59$, $p = .45$), indicating that arithmetic ability did not influence the main effect of dyslexia. All other effects did not reach significance (all *p*s > .19).

Supplementary Table 2

Main effects and interaction effects of the reading task

		Accuracy		Reaction time		Non response	
	df	*F*	*p*	*F*	*p*	*F*	*p*
Condition	1,41	0.06	.816	68.72	< .001	7.15	.011
DL	1,41	3.82	.058	7.31	.010	4.10	.050
DC	1,41	0.21	.646	12.35	.001	0.89	.352
Condition x DL	1,41	1.38	.247	1.27	.266	1.82	.185
Condition x DC	1,41	0.85	.361	1.13	.294	0.17	.684
DL x DC	1,41	2.81	.101	5.69	.022	0.59	.446
Condition x DL x DC	1,41	0.11	.746	1.31	.259	0.39	.537

CHAPTER 5

Numerical magnitude processing and phonological processing in dyscalculia, dyslexia and comorbid dyslexia/dyscalculia

Abstract

Specific learning disorders (i.e., dyscalculia and dyslexia) are very common, as is their comorbidity. It has been suggested that the core cognitive deficit in dyscalculia is an impairment in numerical magnitude processing; similarly, in dyslexia, phonological processing deficits are considered to be the main cognitive deficit. Cognitive theories on comorbid dyslexia/dyscalculia have suggested a number of hypotheses about which cognitive deficits underlie the comorbidity. However, few studies have thus far directly compared the abovementioned domain-specific cognitive correlates of dyscalculia and dyslexia.

In this study, which is part of the larger neuroimaging study presented in the previous chapter, we assessed symbolic and non-symbolic numerical magnitude processing, and three subcomponents of phonological processing, namely phonological awareness, lexical access and verbal short-term memory. The effect of these domain-specific cognitive correlates on dyscalculia and dyslexia was explored.

We did not find an effect of numerical magnitude processing in children with dyscalculia. On the other hand, block design, a domain-general cognitive correlate, was impaired in children with dyscalculia. Children with dyslexia showed impairments on all subcomponents of phonological processing. We found an additive effect for comorbid dyslexia/dyscalculia, indicating that dyscalculia and dyslexia contributed independently to the comorbidity. However, as only a limited number of cognitive variables were assessed in this study due to practical constraints, we should be cautious when interpreting these results.

5.1 Introduction

Specific learning disorders, such as deficits in learning to calculate (dyscalculia) or read (dyslexia) are very common. Research has shown that between 5 and 15 percent of children suffer from dyscalculia or dyslexia (Rapin, 2016). The prevalence of the combination of both, comorbid dyslexia/dyscalculia, is also very high (around 40%; Wilson et al., 2015). In this study, which is part of the neuroimaging study described in the previous chapter, we directly compared the core cognitive deficits of dyscalculia and dyslexia, which are assumed to lie in numerical magnitude processing and phonological processing, respectively. In the remainder of this introduction, we will first discuss the cognitive deficits of dyscalculia and dyslexia, followed by a discussion of the hypotheses explaining the comorbidity. Finally, we will discuss the aims of the present study.

Dyscalculia is characterized by difficulties in arithmetic, more specifically in the development of the use and execution of calculation procedures, and in the retrieval of arithmetic facts from memory, that persist despite remediation and adequate scholastic opportunities and are not better accounted for by global developmental delays (American Psychiatric Association, 2013; Geary et al., 2007). The dominant hypothesis regarding the cognitive deficit associated with dyscalculia is an impairment in processing numerical magnitudes (Ashkenazi et al., 2013; Butterworth, 2011; De Smedt et al., 2013; Mazzocco et al., 2011; Rousselle & Noël, 2007). Typically, numerical magnitude processing is assessed via a number comparison task, in which participants are asked to indicate the numerically larger number of two presented numbers. This number comparison tasks exists in two variants: symbolic (i.e., numbers presented as Arabic digits), and non-symbolic (i.e., using dot arrays) comparison. There are two hypotheses about the origin of these numerical magnitude processing difficulties: The defective number module hypothesis, which claims that deficits originate from an impairment in the representation of numerical magnitudes per se, and the access deficit hypothesis, which postulates that deficits arise from an impairment in accessing the underlying numerical magnitude from symbols. At the behavioral level, evidence in favor of both hypotheses has been reported. More specifically, the defective number module hypothesis predicts difficulties on both symbolic and non-symbolic number comparison tasks in children with dyscalculia, as was the case in studies by for example Landerl, Fussenegger, Moll, & Willburger (2009) and Mussolin, Mejias, & Noël (2010). On the other hand, the access deficit hypothesis predicts impairments in symbolic but not non-symbolic number comparison, as was shown in research by Rousselle & Noël (2007), Iuculano, Tang, Hall, & Butterworth (2008), De Smedt &

Gilmore (2011) and Vanbinst, Ghesquière, & De Smedt (2014). Against this background, we included both a symbolic and a non-symbolic number comparison task in this study to investigate numerical magnitude processing impairments as a main cognitive deficit in children with dyscalculia.

Children with *dyslexia* show deficits in reading abilities, that persist despite targeted interventions and adequate scholastic opportunities, and that are not better accounted for by global developmental delays (American Psychiatric Association, 2013; Snowling, 2005). The most dominant theories about the cognitive origins of these reading deficits postulate that they are attributed to cognitive deficiencies in phonological processing (Snowling, 2005; Stanovich et al., 1994; Wagner & Torgesen, 1987), which can be defined as the ability to decode and manipulate phonemes. At the behavioral level, this deficit in phonological processing causes difficulties in decoding written words into phonemes, which in turns impairs identifying words (Shaywitz & Shaywitz, 2001) and hinders fluent reading. Within the reading literature, phonological processing is subdivided into three subcomponents: phonological awareness, lexical access and verbal short-term memory (Boets et al., 2010; Wagner & Torgensen, 1987). Phonological awareness refers to sensitivity to the auditory structure of language. It is typically measured using phoneme deletion tasks. Lexical access is defined as the speed with which participants can retrieve lexical referents from memory and can be assessed by a rapid automatized naming task. Finally, verbal short-term memory reflects the ability to maintain auditory information online, and can be measured using a digit span task. Various studies have shown that children with dyslexia show deficits in all three subcomponents of phonological processing (see e.g., Boets et al., 2010; Mann & Liberman, 1984). We therefore included tasks tapping into all subcomponents of phonological processing.

Dyscalculia and dyslexia often co-occur; the prevalence of the *comorbid dyslexia/dyscalculia* is high (Landerl & Moll, 2010; Wilson et al., 2015). A number of hypotheses have been postulated to explain this comorbidity. First, the domain-specific cognitive deficit account, or additive account, states that both dyscalculia and dyslexia arise from distinct, domain-specific cognitive correlates (numerical magnitude processing for dyscalculia, phonological processing for dyslexia), and that the deficits in the comorbid group arise as an additive effect of the deficits of both isolated disorders. The results in Landerl et al. (2009) and Moll, Göbel, & Snowling (2015) are in line with this hypothesis. They showed that children with dyscalculia were impaired on symbolic and non-symbolic numerical magnitude processing, but that children with dyslexia were not. On the other hand, children with dyslexia showed impairments in phonological processing, unlike children with dyscalculia. The cognitive deficits found in the comorbid group were the result of an additive effect of dyscalculia and dyslexia. Second, a common deficit account has suggested that deficits in the comorbid group arise from a shared, impaired cognitive correlate that affects both mathematics and reading. One candidate is phonological processing, which obviously affects reading, but which has also been related to mathematics, in particular the ability to retrieve arithmetic facts (e.g., De Smedt, Archibald, Taylor, & Ansari, 2010). This hypothesis is reflected in an under-additive effect, as children from the comorbid group are predicted to be less impaired than the sum of the single deficits. Third, a domain-general account has been proposed, in which domain-general cognitive factors such as working memory, attention and inhibition cause deficits in both reading and arithmetic ability (see Houdé, Rossi, Lubin, & Joliot, 2010; Vellutino, Fletcher, Snowling, & Scanlon, 2004 for a review). Finally, an overarching, multi-factorial model has been suggested, which acknowledges that both domain-general *and* domain-specific correlates underlie comorbidity. A study by Willcutt et al. (2013) found support for this model, by showing that both children with dyslexia and children with dyscalculia showed impairments on working memory (domain-general), but that deficits in set shifting were only found in children with dyscalculia, and impairments in phonological awareness and naming speed only in children with dyslexia (domain-specific). It is important to note that, since we only included domain-specific cognitive correlates, we were only able to investigate the former two hypotheses.

Only a few studies thus far have simultaneously inspected the influence of the core cognitive deficits described in dyscalculia and dyslexia. In the present study, we therefore directly compared the cognitive deficits of children with dyscalculia and dyslexia, similar to a study by Landerl and colleagues (2009). We assessed numerical magnitude processing and three major domains of phonological processing in children with dyscalculia, dyslexia and comorbid dyslexia/dyscalculia, as well as in typically developing children.

5.2 Materials and Methods

5.2.1 Participants

Participants were the same as in Chapter 4 (data were collected during session 1) and comprised 62 children (34 male) aged between 9 and 12 (M = 10.83 years, SD = 0.83). Of these children, 39 children had received a formal diagnosis of a specific learning disorder by a trained clinician, in accordance with DSM-5 criteria (American Psychiatric Association, 2013). These children were classified into three groups: children with dyslexia (DL, $n = 19$), children with dyscalculia (DC, $n = 11$) and children with comorbid dyslexia/dyscalculia (DLDC, $n = 9$). The remaining typically developing children (TD, $n = 23$) had not received a formal diagnosis of a learning disorder. Furthermore, none of the children reported a history of any psychiatric or neurological illness, or had been diagnosed with any additional developmental disorders (e.g., ADHD). All parents gave written consent. the study was approved by the Medical Ethical Committee of KU Leuven.

To validate the clinical diagnoses, we used standardized tests of arithmetic (Tempo Test Arithmetic; de Vos, 1992) and reading ability (One Minute Test; Brus & Voeten, 1979 and Klepel; Van den Bos, Spelberg, Scheepstra, & De Vries, 1994) and administered block design and vocabulary from the WISC-III-NL (Kort et al., 2005) as measures of performance and verbal IQ, respectively (See Figure 5.1 and Table 5.1). As expected, analyses showed that children with dyscalculia were impaired on arithmetic ($F(1,58) = 15.74$, $p < .001$), and that children with dyslexia were not ($F(1,58) = 2.18$, $p = .15$). Children with dyslexia were impaired on reading ($F(1,58) = 50.80$, $p < .001$), contrary to children with dyscalculia ($F(1,58) = 0.23$, $p = .63$). We also found a main effect of dyscalculia on block design ($F(1,58) = 52.70$, $p < .001$) and vocabulary ($F(1,57) = 5.13$, $p = .027$), but no effects of dyslexia ($F(1,58) = 1.34$, $p = .25$ and $F(1,57) = 2.06$, $p = .16$, respectively). None of the interaction effects were significant (all p's > .11). For vocabulary, it is important to note that, although children with dyscalculia scored lower than children without dyscalculia, their scores were close to the population average, indicating that their intellectual abilities were within normal range. Finally, we found no effect of dyscalculia ($F(1,58) = 0.99$, $p = .33$) nor of dyslexia ($F(1,58) = 0.01$, $p = .93$) on age, hence we did not control for age in any of the following analyses.

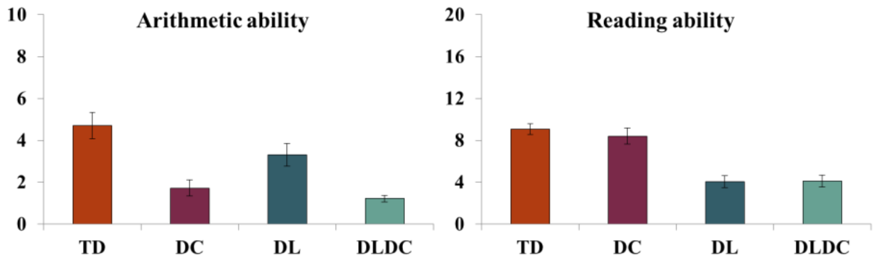

Figure 5.1. Descriptive results on tests of arithmetic ability (decile scores) and reading ability (standardized scores with $M = 10$, $SD = 3$). Error bars indicate the standard error of the mean.

Table 5.1

Means per group of the standardized assessment

	TD	DC	DL	DLDC
Age in years	10.83 $_a$	11.06 $_a$	10.81 $_a$	10.92 $_a$
Block Design $_{(1)}$	13.13 $_a$	8.55 $_b$	12.26 $_a$	8.00 $_b$
Vocabulary $_{(1)}$	11.82 $_a$	11.36 $_b$	11.95 $_a$	9.22 $_b$

Note. TD = typically developing, DC = dyscalculia, DL = dyslexia, DLDC = comorbid dyslexia/dyscalculia; (1) standardized scores: M = 10, SD = 3. For each variable under study, means that share the same index did not differ statistically on a p < .05 level.

5.2.2 Materials

5.2.2.1 Numerical magnitude processing

Numerical magnitude processing was assessed via a non-symbolic and a symbolic number comparison task. Two numbers below 10 (dot arrays for the non-symbolic variant, Arabic digits for the symbolic task) were presented simultaneously on a computer screen, and children were asked to indicate which of the two numbers (left or right) was numerically larger by pressing either the ‘d’ (left) or ‘k’ (right) key. The position of the larger number was counterbalanced. All combinations of numbers 1 to 9 were used, resulting in 72 trials in total Each trial consisted of a fixation point (200 ms), after which the stimulus appeared and remained on the screen until a response was detected. The non-symbolic stimuli were generated using a Matlab script (Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004) and were controlled for non-numerical parameters, such as dot size, density and total occupied area. For both tasks, an inverse efficiency score (which is calculated by dividing reaction time by accuracy) was used in analyses.

5.2.2.2 Phonological processing

The three subcomponents of phonological processing (i.e., phonological awareness, lexical access, and verbal short-term memory; see Wagner & Torgensen, 1987), were assessed in this study. To measure *phonological awareness*, a phoneme deletion task was administered (Bart Boets et al., 2010). In this task, children heard a phoneme (e.g., [r]) followed by a non-word (e.g., *vrik*). Consequently, they were instructed to repeat the non-word, leaving out the phoneme (e.g., *vik*). The number of correctly solved trials (out of a possible 30) was used in analyses. *Lexical access* was measured via the rapid automatized naming task (Van den Bos, Zijlstra, & Van den Broeck, 2003), in which children were asked to read aloud 50 stimuli of a specific category (objects, colors, digits and letters) as fast and as accurate as possible. The average time it took children to name all the items of each category was used in analyses. Finally, *verbal short-term memory* was assessed using the digit recall forwards task, in which children were asked to repeat an auditory presented sequence of digits in the correct order (De Smedt et al., 2009). The task started with three trials with a sequence length of two digits. One digit was added to the sequence if the child recalled at least two of the three trials of the same sequence length correctly. Of each sequence length, three trials were presented. The number of correctly repeated digit sequences was used in analyses.

5.2.3 Procedure

Testing took place in a quiet room in the Psychology department of KU Leuven. All children were tested individually on the described cognitive factors. Tests measuring arithmetic ability, reading ability, intelligence and lexical access were administered using paper-and-pencil tasks, numerical magnitude processing tests were computerized and designed using Matlab, and phonological awareness and verbal short-term memory were assessed using a recorded, standardized auditory presentations of phonemes and words or digits, respectively. Note that the ordering used in this description was also the ordering in which tests were administered.

5.2.4 Analyses

Behavioral data were analyzed using SPSS (IBM SPSS Statistics 23; IBM Corp., Chicago, IL, USA). A 2x2 ANOVA with the presence of dyscalculia and the presence of dyslexia as between-subject factors was performed on each of the cognitive correlates. A non-significant interaction effect will point towards an additive effect of dyslexia and dyscalculia, whereas a significant interaction effect will indicate an over or under additive effect, in which dyslexia and dyscalculia would not contribute independently to the comorbidity. A Bonferroni correction was applied in all these analyses to control for multiple comparisons. Furthermore, to simultaneously investigate the contributions of intelligence, numerical magnitude processing and phonological processing to the presence of dyscalculia, dyslexia and comorbid dyslexia/dyscalculia, a multinomial logistic regression analysis was performed in which diagnosis was predicted based on intelligence and the cognitive correlates. This type of analysis allowed us to directly compare the predictive value of all variables on the presence of the diagnosis.

5.3 Results

5.3.1 Descriptive statistics and group comparisons

Descriptive statistics on the domain-specific cognitive correlates are presented in Table 5.2. Data from one participant was missing for vocabulary, data from one participant for non-symbolic numerical magnitude processing, and data from one participant for phonological awareness and verbal short-term memory. To test whether the different groups of children with learning disorders differed on the cognitive correlates considered in this study, we ran 2x2 ANOVAs with dyslexia and dyscalculia as between-subject variables (see Table 5.3 for a detailed overview of the results).

Table 5.2

Descriptive statistics of the cognitive correlates

	TD	DC	DL	DLDC
Symbolic numerical magnitude processing				
M	840.53	922.10	857.91	864.76
SD	111.95	227.84	161.56	286.15
Non-symbolic numerical magnitude processing				
M	1246.06	1448.99	1509.10	1440.42
SD	320.17	468.66	582.21	730.64
Phonological awareness				
M	24.27	22.36	18.53	18.78
SD	4.15	4.11	6.79	4.15
Lexical access				
M	35.86	35.11	39.29	38.42
SD	5.80	7.84	7.76	5.35
Verbal short-term memory				
M	11.68	12.18	10.05	9.44
SD	2.17	2.04	2.41	1.13

Note. TD = typically developing, DC = dyscalculia, DL = dyslexia, DLDC = comorbid dyslexia/dyscalculia.

In contrast to our expectations, children with and without dyscalculia did not differ on symbolic or non-symbolic numerical magnitude processing (see Table 5.3). Furthermore, children with dyslexia (i.e., DL and DLDC) performed more poorly compared to children without dyslexia (i.e., DC and TD) on phonological awareness and verbal short-term memory. There was a trend towards children with dyslexia being slower than children without dyslexia on lexical access, but this trend did not reach significance. A more detailed glance into this measure showed that children with and without dyslexia were equally fast in naming colors, objects and digits (all p's > .13), but that children with dyslexia were significantly slower in naming letters (p = .013). Finally, we found no significant interaction effects on either of the domain-specific cognitive factors included in this study. In other words, none of the cognitive factors was the effect of dyscalculia influenced by the presence of dyslexia, or vice versa.

Table 5.3

Main and interaction effects of ANOVAs

		DC		DL		DL x DC	
	df	*F*	*p*	*F*	*p*	*F*	*p*
Symbolic numerical magnitude processing	1,58	0.79	.38	0.16	.69	0.57	.46
Non-symbolic numerical magnitude processing	1,57	0.12	.74	0.60	.44	1.27	.27
Phonological awareness	1,57	0.35	.56	11.05	< .01	0.59	.45
Lexical access	1,58	0.19	.66	3.33	.07	0.01	.97
Verbal short-term memory	1,57	0.01	.93	14.17	< .01	0.91	.34

Note. DC = main effect of dyscalculia, DL = main effect of dyslexia, DL x DC = interaction effect between dyslexia and dyscalculia.

5.3.2 Logistic regression

We also attempted to predict the presence of a diagnosis (dyslexia, dyscalculia or comorbid dyslexia/dyscalculia) based on all the variables included in this study by means of multinomial logistic regression. As previously noted, we found differences in block design and vocabulary between groups. Therefore, we included these domain-general variables as well as the domain-specific cognitive correlates (i.e., numerical magnitude processing and phonological processing) in the model, to inspect which variables discriminated best between the groups of children with learning disorders. All assessed variables were added into the model using a forward stepwise approach. This analysis showed that block design, vocabulary, phonological awareness and verbal short-term memory contributed significantly to the model (all p's < .05). Symbolic and non-symbolic numerical magnitude processing, as well as lexical access did not contribute significantly. We further observed that block design was a significant predictor for dyscalculia (p = .002) and for comorbid dyslexia/dyscalculia (p = .007); phonological awareness was a significant predictor for dyslexia (p = .022). Both vocabulary (p = .072) and verbal short-term memory (p = .064) were marginally significant predictors for comorbid dyslexia/dyscalculia. All predictors were negatively associated with the presence of the diagnoses, i.e., the lower the performance on the tests, the more likely that a diagnosis had been set, as was expected.

5.4 Discussion

In this study, we investigated the influence of two domain-specific cognitive correlates (i.e., numerical magnitude processing and phonological processing) on dyscalculia, dyslexia, and comorbid dyslexia/dyscalculia in children aged 9 to 12. We will first discuss the effects found per domain-specific cognitive correlate, followed by a discussion on which factors attributed the comorbidity. Finally, limitations of the current study will be discussed, as well as suggestions for future research.

In contrast to our expectations, we did not find an effect of *numerical magnitude processing* on dyscalculia. It is surprising that children with dyscalculia were not impaired on symbolic or non-symbolic numerical magnitude processing, when there is evidence in the literature that (especially symbolic) numerical magnitude processing is very relevant for the development of arithmetic skills (see e.g., Vanbinst, Ansari, Ghesquière, & Smedt, 2016) and that children with dyscalculia are often impaired in numerical magnitude processing (Butterworth, 2011; De Smedt et al., 2013; Piazza et al., 2010). The lack of impairment on numerical magnitude processing in children with dyscalculia could potentially be explained by the nature of the task used to measure numerical magnitude processing: a number comparison task that only included numbers below 10. Mazzocco et al. (2011) and Piazza et al. (2010) showed deficits on a non-symbolic number comparison task in children with dyscalculia, but used larger dot arrays (20 to 50 dots) compared to the current study (1 to 9 dots). For the symbolic number comparison task, it is possible that processing such small numbers is already strongly automatized in children 9 to 12 year old children, even in those with dyscalculia. Recently, Brankaer, Ghesquière, & De Smedt (2016) have reported differences in performance between typically developing children and children with dyscalculia on a symbolic number comparison task in all grades primary school, except Grade 6 (11-12 year old children), potentially also reflecting the automatized processing of small numbers in children with dyscalculia from around 11 years old onwards. It is therefore possible that with more difficult numerical magnitude processing tasks, differences between children with and without dyscalculia might be observed. One example could be a 2-digit number comparison task (Mundy & Gilmore, 2009).

Turning to *phonological processing*, our results showed that children with dyslexia performed worse on phonological awareness and verbal short-term memory compared to children without dyslexia. We did not find an effect of lexical access, but an additional analysis pointed out that children with dyslexia were impaired on letter naming, yet not on digit, color or object naming. The results from the logistic regression indicated that phonological awareness was a significant contributor to the presence of dyslexia, but that lexical access and verbal short-term memory were not.

The effect of phonological processing on dyslexia is in line with previous literature (see also Landerl et al., 2009). Mann & Liberman (1984) already reported deficits in phonological awareness and in verbal short-term memory in children with dyslexia, and Fawcett & Nicolson (1994) showed impaired naming speed in children with dyslexia (see also Melby-Lervåg, Lyster, & Hulme, 2012 for a meta-analysis). However, whereas we only found an effect of letter naming speed in the current study, Fawcett & Nicolson (1994) reported slower naming speed in colors and digits as well, in children aged 8, 13 and 17 years old, and Willburger and colleagues (2008) reported that children with dyslexia showed deficits in naming digits, letters, objects and colors. The children included in Willburger et al. (2008) were similar in age compared to the children included in the current study, yet our findings do not confirm these results.

Dandache, Wouters and Ghesquière (2014), reported that both phonological awareness and lexical access significantly predicted reading ability throughout primary education, including in sixth grade (i.e., in children similar in age as in the current study). In the current study we only replicated these findings for phonological awareness, but not for lexical access.

Similar to the results reported by Landerl and colleagues (2009), we did not find an effect of phonological processing on dyscalculia. Willburger, Fussenegger, Moll, Wood, and Landerl (2008) reported impairments in 8 to 10 year old children with dyscalculia on digit naming, however we did not replicate that finding. This might be explained by the fact that our participants were slightly older, and that the processing of symbolic numbers might have been already automatized in our sample. Note that this was also suggested as a reason for the lack of effect of numerical magnitude processing (see previous paragraph).

We found no significant interaction effects between dyscalculia and dyslexia, similar to the findings reported in Landerl and colleagues (2009). This lack of significant interaction effects suggested that the deficits observed in children with comorbid dyslexia/dyscalculia were additive, resulting from a combination of two separate cognitive profiles. However, by only assessing domain-specific cognitive correlates, it is only possible to investigate the additive and under-additive accounts of comorbid dyslexia/dyscalculia.

Although we did not include measures of, for example, working memory or attention, we did assess one domain-general cognitive correlate, namely intelligence. We found that children with dyscalculia were impaired on both block design and vocabulary compared to children without dyscalculia. Furthermore, the presence of dyscalculia, as well as of comorbid dyslexia/dyscalculia was predicted by children's scores on block design.

The impairment of children with dyscalculia on block design has been observed in previous research (see e.g., Berteletti, Prado, & Booth, 2014; Kucian et al., 2011), and might be explained by the heavy reliance on spatial processing skills and working memory in this task, which have found to be impaired in children with dyscalculia (e.g., Rotzer et al., 2009; Szucs, Devine, Soltesz, Nobes, & Gabriel, 2013).

The impairment of children with dyscalculia on vocabulary was rather unexpected, but it is important to note that their intellectual abilities were within the normal range, albeit lower than those of children without dyscalculia. Vocabulary was also found to contribute (marginally significantly) in predicting comorbid dyslexia/dyscalculia. This is potentially due to the fact that, although both groups of children with dyscalculia (DC and DLDC) performed worse on vocabulary compared to children without dyscalculia (DL and TD; see Table 1), children with comorbid dyslexia/dyscalculia ($M = 9.22$) scored even lower, albeit only marginally significant, compared to children with isolated dyscalculia ($M = 11.36$, $p = .052$). This finding indicates a possible overadditive effect for vocabulary: children with comorbid dyslexia/dyscalculia performed lower than expected based on the scores of children with isolated dyslexia and children with isolated dyscalculia. However, this potential effect remains to be investigated in more detail.

Future studies investigating the domain-specific cognitive correlates of dyslexia, dyscalculia and comorbid dyslexia/dyscalculia might benefit from addressing some of the limitations of the current study. First, the sample size in the current study is rather small. However, as this study is part of a larger neuroimaging project, recruiting children was more difficult than in a standard behavioral study. Second, we only included a limited number of cognitive correlates in this study due to practical constraints of the project as a whole. It would however have been interesting and beneficial for the study to include tasks that tap into a wider range of domain-general cognitive correlates potentially involved in dyslexia and/or dyscalculia, such as working memory, attention and inhibition (see e.g., Ashkenazi, Rubinsten, & Henik, 2009; Facoetti, Turatto, Lorusso, & Mascetti, 2001; Schuchardt, Maehler, & Hasselhorn, 2008).

In conclusion, the results presented in the current study indicate that children with dyscalculia were not impaired on symbolic or non-symbolic numerical magnitude processing, likely due to task effects, but did show deficits in block design, a domain-general cognitive correlate. Deficits in phonological processing were found in children with dyslexia. The cognitive deficits for children with comorbid dyslexia/dyscalculia were additive in nature, suggesting that dyslexia and dyscalculia are independently contributing cognitive profiles. Our results seem to be in line with the multi-factorial model of comorbidity, acknowledging the contribution of both domain-specific (here phonological processing) and domain-general (here block design) cognitive factors in comorbid dyslexia/dyscalculia. However, as we only included a limited number of cognitive correlates, these results should be interpreted with caution. Future studies could benefit from assessing a more elaborate testing battery of domain-general cognitive correlates (e.g., working memory, inhibition, attention).

CHAPTER 6

General discussion

Arithmetic constitutes a large part of our lives; We perform simple additions, subtractions, multiplications and divisions on a daily basis. Nonetheless, the neural correlates of arithmetic in adults and in children with or without learning disorders are not yet fully understood. The aim of this doctoral dissertation was to supplement detected gaps in the literature, using state of the art multivariate pattern analysis techniques.

In this general discussion, I will first provide a summary and discussion of the main findings and the theoretical implications of the studies described above. Furthermore, I will discuss some methodological considerations, and finally I will offer suggestions for potentially fruitful future research.

6.1 Main findings and theoretical implications

6.1.1 The visual code during arithmetic in adults

In the first study (***Chapter 2***) we looked into the neural correlates of the visual code in the context of arithmetic. The involvement of the visual code during arithmetic problem solving had been well established (see Menon, 2015 for a review), yet the specific role and anatomical location of this code remained unclear. Therefore, we investigated to which extent there is a focal region in the occipitotemporal cortex specifically tuned for the processing of Arabic digits during arithmetic, as well as how the processing of digits emerges throughout the ventral visual processing stream.

Using univariate analyses, we localized a region in the lateral occipital cortex that was activated more by subtracting digits than by subtracting number words. As digits and number words are both symbolic formats that clearly differ in the involvement of the visual code, this contrast between conditions seemed appropriate to localize the visual code. At first glance, we found a focal region specifically dedicated to processing digits. The existence of such a region is not surprising, as previous research has shown similar focal preferences for other visual categories, such as objects (Grill-Spector et al., 2001), faces (Kanwisher, McDermott, & Chun, 1997) and words (Baker et al., 2007). However, the preference for digits in this [digits – words] region was not replicated in an additional experiment, indicating that this region is *not* specifically tuned for digits.

Previous research that aimed to find a brain region hosting the visual code is limited, and had resulted in mixed findings (Park, Hebrank, Polk, & Park, 2011; Pinel & Dehaene, 2013; Polk et al., 2002; Shum et al., 2013). A critical difference between these previous studies and the current study is that we controlled for potential confounding effects using a second, control experiment. As number words by definition consist of more visual elements (i.e., multiple letters) compared to digits (i.e., one or two characters), and as visual regions can be sensitive to the amount of visual information that is presented (Xu & Chun, 2006; Xu, 2008), we controlled for the amount of visual information presented by creating letter and digit strings of equal length in the control experiment. Furthermore, to exclude the possibility that task-dependent effects were at the root of the specificity of this focal region, rather than a preference to the symbol itself, a non-arithmetic, order judgment task was used. By controlling for these confounding factors, we found that our potential focal region dedicated to processing digits was likely a task- or stimulus-related effect.

Using multivariate correlational analyses, we also looked into the evolution in the processing of digits throughout the ventral visual stream. We found that, where primary visual cortex clustered digits and letters based on the number of characters on the screen, more high-level regions such as the visual word form area clustered visual information based on stimulus category (i.e., distinct representations for digits and letters). This alteration in the representation of a visual stimulus category throughout the visual system had already been reported for objects in general (see Op de Beeck, Haushofer, & Kanwisher, 2008), and is now replicated for digits specifically. It however indicates that distinguishing between letters and digits (which is assumed to be the role of the visual code) might occur in terms of distributed patterns of activation rather than in one focal region specifically. The visual code might therefore be distributed across the ventral visual processing stream, rather than located in one specific focal region.

6.1.2 The neural correlates of arithmetic in typically developing children

In Study 2 (***Chapter 3***), we investigated the neural correlates of arithmetic in typically developing children. In contrast to previous neuroimaging studies in children, we used a subtraction task in which arithmetic problems were presented using various formats: dot arrays, Arabic digits or number words. This multiple-format paradigm had two main advantages compared to tasks used in previous research: It allowed us to look into all three codes of arithmetic simultaneously, and it allowed us to investigate the neural correlates of strategy use (procedural vs. retrieval) while avoiding confounds such as differences in operation (e.g., subtraction and multiplication; e.g., Prado, Mutreja, & Booth, 2014) and differences in problem size (e.g., small and large additions; e.g., De Smedt, Holloway, & Ansari, 2011).

In line with previous literature, we found that a whole brain network was recruited during arithmetic in children: superior and inferior parietal lobules, bilateral occipital regions, fusiform gyrus, inferior and medial frontal gyrus, cingulate cortex, anterior insula, and precentral gyrus. When looking specifically into differences between presentation formats, we found that symbolic formats (i.e., Arabic digits and number words) did not differ in terms of the regions they recruited, apart from more activation in primary visual cortex for number words compared to digits, which might be attributed to the amount of visual information on the screen (i.e., more visual elements for number words). Symbolic and non-symbolic formats on the other hand, differed vastly in the neural response they elicited. Whereas non-symbolic items showed increases in activity in the superior parietal lobule and superior frontal gyrus, arithmetic in symbolic items showed larger activity in angular gyrus, supramarginal gyrus and middle temporal gyrus. The neuroanatomical locations of regions that showed increased activation levels during symbolic and non-symbolic items correspond to the direct and the indirect route of calculation, respectively, described by Dehaene and Cohen (1997). They also overlap with the regions described in Prado et al. (2014): Regions activated more by non-symbolic than by symbolic formats correspond to the areas activated during their number processing localizer task (which taps into the magnitude code), while regions activated more by symbolic than by non-symbolic formats coincide with the regions activated in their phonological localizer (which corresponds to the verbal code). Prado et al. (2014) suggested that this difference in activated networks might be due to differences in strategy use (procedural strategies for numerical areas, arithmetic fact retrieval for phonological areas). This might also be the case in our study. To avoid the risk of reverse inference (i.e., directly inferring the involvement of cognitive processes from the activation in specific neural regions, see Poldrack, 2006), we investigated this hypothesis by collecting additional behavioral data. Specifically, we used trial-by-trial verbal self-reports to validate the hypothesis that, in our study, symbolic subtractions were solved with fact retrieval, and non-symbolic subtractions with procedural strategies. Verbal self-reports have been found to a reliable manner to measure arithmetical strategy use (Siegler & Stern, 1989), although they are easily biased by instructions (Kirk & Ashcraft, 2001). To avoid retest effects and due to practical considerations, we collected these strategy reports in a different sample of children. Both groups of children did not differ in age, arithmetic ability or reading ability. The hypothesis that symbolic subtractions would be solved with fact retrieval, and non-symbolic subtractions with procedural strategies was confirmed in this additional behavioral study. In a follow-up study by Polspoel, Peters and De Smedt (under review), we collected verbal strategy reports in children that also participated in an imaging study. The results from this study indicated that, indeed, arithmetic problems solved with fact retrieval activated the network found to be active for symbolic formats in the current study, whereas arithmetic problems solved with procedural strategies activated the network activated for non-symbolic formats.

Although the fMRI-experiment in ***Chapter 3*** was controlled for differences in operations and problem size, the paradigm was not controlled for task difficulty. Behavioral analyses pointed out that children showed lower accuracies in subtractions presented as dot arrays compared to digits and number words. This implicates that task load was different for non-symbolic than for symbolic subtractions. It should be noted that the regions found to be more active for subtractions in non-symbolic formats correspond to regions described as being part of the multiple-demand network (Fedorenko et al., 2013), a network which is activated more strongly with increasing task load. On the other hand, the regions found to be more active for subtraction in symbolic formats, coincide with regions described as being part of the default mode network (Raichle et al., 2001), a network which is activated more strongly with *decreasing* task load. Although these networks have been well-described, this alternative hypothesis has been generally overlooked in the literature on numerical cognition and should be considered more in future research. However, because we used a block design, we were unable to discard incorrectly solved trials and by extension to equalize performance level over conditions to control for task difficulty.

The results from Study 2, in which only subtraction items were used, clearly show that, while previous studies have investigated the neural correlates of strategy use by contrasting different operations, it is not the operation per se, but rather the characteristics of the specific arithmetic problem that determine the strategy to solve it. By extension, the neural response elicited is dependent on the characteristics of the arithmetic problems. Furthermore, it is also important to keep in mind that the strategy children use to solve an arithmetic problem depends on the emphasis put on fact retrieval by the math curriculum. Behavioral studies have reported cross-cultural differences in strategies use (Campbell & Xue, 2001), hence it would be very interesting to inspect the neural correlates of these cross-cultural differences.

Finally, although we pointed out the similarity between our results and the neural correlates of the direct and indirect route suggested by Dehaene and Cohen (1997), we would like to note that caution is required when applying neural models based on adult or patient data (such as the Triple Code Model) on neuroimaging data in children (see Ansari, 2010). The use of adult models in children for example assumes that similar neural regions are recruited in children and in adults. However, the neural correlates of arithmetic undergo a frontal-to-parietal shift with development (Rivera et al., 2005; Rosenberg-Lee, Barth, et al., 2011) that is not accounted for by an adult model like the Triple Code Model. This development is comparable to findings in other academic skills, such as reading. The reading literature has consistently reported a shift towards increasing functional specialization of the left hemisphere with age (see Eden, Olulade, Evans, Krafnick, & Alkire, 2016 for a review; Shaywitz et al., 2007). Similarly, the verbal code is claimed to be located in the left hemisphere according to Dehaene and Cohen (1997), yet this lateralization might not have developed yet in children. The results from the current study, for example, show increased activation for digits and words in both left and right angular gyri and inferior parietal cortices, and in right supramarginal gyrus. Although it is clear that adult models can guide predictions regarding the neural correlates of arithmetic in children, it is important to specifically investigate the development of arithmetic processing in children. Only by investigating the neural correlates of typical development, can we gain more insight into the neural correlates of atypical development.

6.1.3 The neural and cognitive correlates of arithmetic in dyscalculia and dyslexia

Difficulties in solving arithmetic are an inherent part of dyscalculia (Geary et al., 2007, 1987). However, difficulties in specific parts of arithmetic, namely retrieving arithmetic facts and processing symbolic magnitudes have been reported in dyslexia as well (see Moll, Göbel, & Snowling, 2015). Furthermore, the comorbidity between dyslexia and dyscalculia is remarkably high (around 40%; see Wilson et al., 2015). Nonetheless, the neural correlates of arithmetic in dyslexia and dyscalculia have never been directly contrasted, and the neural correlates of their comorbidity are even uninvestigated to date. In Study 3 (***Chapter 4***), we investigated the neural correlates of these learning disorders in the context of arithmetic. In Study 4 (***Chapter 5***), we directly compared the cognitive correlates of dyslexia and dyscalculia.

The study described in ***Chapter 4*** was the first study in which children with dyslexia, children with dyscalculia and children with comorbid dyslexia/dyscalculia were directly compared in terms of their neural profiles. All children performed the subtraction task in three formats (see ***Chapter 3***) while fMRI data were collected.

At the behavioral level, the results were in line with what was expected: Children with dyscalculia and children with comorbid dyslexia/dyscalculia performed poorly on all formats, yet most outspoken on dot arrays. Children with dyslexia showed impairments during arithmetic in symbolic formats (i.e., digits and number words). At the neural level, univariate analyses pointed out that all children with learning disorders showed hypo-activation compared to typically developing children in a whole brain network (frontal, parietal, occipital and temporal areas), which converges with studies in previous studies on arithmetic in children with dyscalculia (see e.g., Ashkenazi, Rosenberg-Lee, Tenison, & Menon, 2012; Berteletti, Prado, & Booth, 2014). Strikingly, regions lower in activation in children with dyscalculia compared to typically developing children were remarkably similar in their anatomical locations compared to those regions that showed lower activity in children with dyslexia. Furthermore, a direct comparison between children with dyslexia and children with dyscalculia revealed that they did not differ in terms of neural activation. Although this finding might point towards neural similarity between dyslexia and dyscalculia in the context of our task, this null-result could also be due to power issues given the rather small sample size ($n_{\text{dyslexia}} = 14$, $n_{\text{dyscalculia}} = 8$).

To circumvent this potential power issue, we performed a multi-variate subject generalization analysis, in which we statistically quantified the similarity between children with dyscalculia, children with dyslexia and children with comorbid dyslexia/dyscalculia in terms of their neural activation patterns (see section 1.4). In line with the surprising univariate results, these multivariate analyses revealed that the neural activation patterns of children with learning disorders are interchangeable, regardless of their diagnosis (dyscalculia, dyslexia or comorbid dyslexia/dyscalculia), and hence that the neural profiles of dyscalculia, dyslexia and comorbid dyslexia/dyscalculia are similar in the context of our arithmetic task. Even more so, the children in this study also performed a reading task during fMRI data acquisition, and the results from those univariate and multivariate subject generalization analyses confirmed the findings from the arithmetic task, albeit less strongly (probably due to power, as the subject sample included in the analyses of the reading task was even smaller because the reading task was performed at the end of the scanning sequence). Collectively, these results point towards neural similarity between dyslexia, dyscalculia and comorbid dyslexia/dyscalculia on a more general level than merely in the context of arithmetic. It is important to note that these findings did not come from null-results, but from a statistically significant test of similarity between groups of children with different learning disorders.

Various explanations might account for these findings. First, differences in performance level and slower reaction times point towards a difference in experienced task difficulty between children with and without learning disorders. The hypo-activation reported in children with learning disorders might possibly be the result of a less efficient modulation of neural activation with increasing task difficulty. However, when assessing the neural correlates of arithmetic in a population that shows deficits in arithmetic ability, this difference in experienced task difficulty is inherent. Second, the hypo-activation and neural similarity reported in children with learning disorders might also be explained by the influences of task-independent, domain-general cognitive factors, such as working memory or attention. Previous research already indicated that children with dyscalculia and/or dyslexia show impairments in these domain-general resources (see e.g., Ashkenazi, Rubinsten, & Henik, 2009; Facoetti, Turatto, Lorusso, & Mascetti, 2001; Schuchardt, Maehler, & Hasselhorn, 2008). However, as we did not include measures of executive functioning in this study, we cannot exclude this possibility. Third, the similarity between the three groups of learning disorders under study fits with the so-called generalist genes hypothesis of learning disabilities (Plomin & Kovas, 2005). This hypothesis postulates that there is a shared genetic influence on academic skills, such as arithmetic and reading (Krapohl et al., 2014; Light & DeFries, 1995; Mascheretti et al., 2014; Plomin & Kovas, 2005), which might similarly affect the neurobiological origin of dyscalculia, dyslexia and comorbid dyslexia/dyscalculia. Fourth, the current findings also somewhat reflect the approach used in the DSM-5, which advocates that there is one category of learning disorders with a similar symptom: difficulties in learning and using academic skills (American Psychiatric Association, 2013), although the DSM-5 allows for the possibility of specifiers. Finally, based on the current findings, we cannot exclude the possibility of specific neurobiological differences between dyscalculia and dyslexia, in addition to the shared atypical activation profile. It is possible that the arithmetic and reading tasks included in this study simply lacked the specificity to pick up other effects.

In Study 4 (***Chapter 5***), we evaluated the same children as in Study 3 (***Chapter 4***) also on the key domain-specific deficits associated with dyscalculia and dyslexia: numerical magnitude processing and phonological processing, respectively. We found that children with dyscalculia were not impaired on either symbolic or non-symbolic numerical magnitude processing, despite evidence in the literature that deficits in numerical magnitude processing are associated with dyscalculia (Butterworth, 2011; De Smedt et al., 2013; Mazzocco et al., 2011; Rousselle & Noël, 2007). They were also not impaired on phonological processing, but did show deficits in the block design subscale of the WISC. Children with dyslexia on the other hand were, as expected, impaired on all investigated subcomponents of phonological processing: phonological awareness, lexical access (more specifically letter naming) and verbal short-term memory, but not on numerical magnitude processing. Finally, the deficits observed in children with comorbid dyslexia/dyscalculia were additive, indicating that dyslexia and dyscalculia contributed independently to the comorbidity. This additivity points towards dyslexia and dyscalculia having distinct behavioral profiles.

The lack of a deficit found in children with dyscalculia in processing symbolic and non-symbolic numerical magnitudes might be due to the fact that we used a single digit number comparison task. It is possible that numerical magnitude processing was already automatized in our subject sample of 9 to 12 year old children, even in those with dyscalculia. Brankaer, Ghesquière and De Smedt (2016) recently reported differences between children with and without dyscalculia on a 1-digit symbolic number comparison task throughout primary school. However, these differences got smaller with age and had disappeared by Grade 6. On a non-symbolic number comparison task, differences between children with and without dyscalculia have been found with larger dot arrays (20 to 50 dots) than in our study (1 to 9 dots; Mazzocco et al., 2011; Piazza et al., 2010), indicating that future research in children of this age range might benefit from using more difficult tasks, such as symbolic and non-symbolic number comparison tasks including larger magnitudes.

Furthermore, we did not include any domain-general correlates, such as working memory, inhibition or attention, although some studies have reported impairments in dyscalculia and dyslexia (Ashkenazi t al., 2009; Facoetti, Paganoni, Turatto, Marzola, & Mascetti, 2000; Reiter, Tucha, & Lange, 2005; Schuchardt et al., 2008; Szucs, Devine, Soltesz, Nobes, & Gabriel, 2013; van der Sluis, de Jong, & van der Leij, 2004; Zhang & Wu, 2011). As our testing battery was very limited due to practical considerations, we should be cautious in interpreting these results. Future research on the cognitive correlates of specific learning disorders should include a more extended range of tasks tapping a more extended range of cognitive correlates.

Combining the results from the neuroimaging (Study 3) and the behavioral study (Study 4), we have found that, despite clear differences in the behavioral profiles of children with dyscalculia, dyslexia and comorbid dyslexia/dyscalculia, the neural profiles of children with learning disorders are remarkably similar. These findings might entail some implications for the way that atypical development is currently investigated. The similarity in neural profiles between children with various specific learning disorders is rather unexpected, given the fact that studies thus far have all focused upon unraveling the neurobiological origin of single disorders and single deficits. Previous studies have often not considered the possibility that the detected neural differences between typically developing children and children with learning disorders reflect something other than specific neural correlates of the disorder under research.

6.2 Methodological considerations

Although we believe that the studies described in this doctoral dissertation on the neural correlates of arithmetic were relevant and important from a theoretical point of view, a major strength of our work lays in some methodological innovations used.

First and foremost, the use of multivariate analyses throughout this doctoral dissertation is a major strength. As already described in the introduction of this dissertation, the use of multivariate analyses tackles some of the drawbacks of using univariate analyses, such as the risk of averaging out effects over voxels. The results from both ***Chapters 2 and 4*** benefited from the use of these multivariate analyses. In ***Chapter 2***, the performed univariate analyses only revealed stronger or weaker activation levels for digits in pre-defined regions of interest. However, using multivariate correlational analyses, we found that distinguishing between letters and digits (which is the role of the visual code) occurs in terms of distributed patterns of activation rather than in one specific region. This indicates that digits and letters might be processed qualitatively differently throughout the ventral visual processing stream. Even more, in ***Chapter 4*** we detected a surprising amount of neural similarity between children with various specific learning disorders with subject generalization analyses. It is important to note that, while the univariate analyses revealed no differences in activation levels between children with learning disorders (which is a null-result that was potentially due to power issues), the multivariate analyses demonstrated this neural similarity using a significant statistical test. Clearly, the use of these state of the art, fine-grained multivariate analyses showed us effects and results that were hidden or under-powered in the univariate analyses, which pleads for more frequent use of these multivariate analyses, also in the context of studying the neural correlates of learning disorders. In the context of studying dyslexia and ADHD, multivariate analyses have already been applied (see e.g., Boets et al., 2013; Fair, Bathula, Nikolas, & Nigg, 2012; Hoeft et al., 2011; Tanaka et al., 2011), however, in the context of dyscalculia this was the first study. Directly contrasting the neural correlates of developmental disorders, as we did in ***Chapter 4***, has proven to be very valuable in this doctoral dissertation and can be a fruitful method in future studies that aim at investigating the specificity or generality of neural correlates of developmental disorders.

Second, in all imaging studies included in this doctoral dissertation, a similar fMRI paradigm was used: a subtraction task in different formats (dot arrays, Arabic digits and number words). In the adult study (***Chapter 2***), all subtractions were below 20, in the children studies (***Chapters 3 and 4***), all subtractions were below 10. Furthermore, adults were asked to indicate whether the result of the subtraction was smaller or larger than a reference magnitude, whereas children were asked to indicate whether the result of the subtraction equaled a reference magnitude. These changes were introduced to ensure that children would be able to perform the task. The paradigm comes with both strengths and weaknesses.
On the plus side, the use of three presentation formats allowed us to look into the visual code of arithmetic introduced in the Triple Code Model (Dehaene & Cohen, 1995) in more detail. This was achieved by contrasting the neural response to digits with the neural response to number words. These symbolic formats differed mainly in their visual characteristics, therefore subtracting their neural responses allowed us to gain more insight into the processes occurring in the ventral visual processing stream during the presentation of digits specifically. As all other aspects of the task (e.g., comparing the result of the subtraction to the reference magnitude) were exactly the same over formats, this was a clean contrast of the effect of digits on visual processing. Second, this paradigm is appropriate in the context of ***Chapter 4***, as it specifically taps into the deficits assumed to be associated with dyscalculia and/or dyslexia. As it is an arithmetic task, children with dyscalculia would by definition perform worse compared to typically developing children. However, as we also used number words as stimuli, we expected that children with dyslexia would have difficulties with that format. We did not expect children with dyslexia to show impairments in calculating with dot arrays, as previous studies had shown that children with dyslexia only show impairments on symbolic, but not on non-symbolic aspects of arithmetic (see e.g., De Smedt & Boets, 2010; Moll et al., 2015). The variation included in this paradigm therefore seemed appropriate for the research

questions addressed in this dissertation. Finally, we specifically chose to stay within one operation and opted for subtraction, as subtraction allows for more variation in strategy use compared to addition and multiplication (Barrouillet, Mignon, & Thevenot, 2008). Differences in those strategies are therefore not attributable to operation specifically.

On the other hand, the paradigm also comes with some drawbacks. First, it is a rather complex task, with both arithmetic (subtraction) and numerical magnitude processing (comparison to the reference magnitude) components. However, these number processing correlates were exactly the same over presentation formats, and were therefore subtracted out whenever the neural contrast between formats was calculated. Second, although the task (i.e., subtraction) is very common for children and adults, the non-symbolic presentation format is not. Generally, we perform subtractions that are presented as Arabic digits, or possibly as number words in the context of word problems. Subtractions presented as dot arrays however, are not part of the math curriculum, and certain findings reported in this dissertation could be confounded by the novelty of calculating using dot arrays. However, it is important to note that, although performance levels were lower when participants were asked to calculate using dot arrays, they were still well above chance level, indicating that both adults and children (even children with learning disorders) were able to perform the non-symbolic subtractions. Third, the visual characteristics of the three presentation formats are, by definition, very dissimilar. Number words and dot arrays consist of more visual elements than Arabic digits, which was evidenced by higher activity levels for number words and dot arrays than for digits in primary visual cortex (see ***Chapters 1 and 2)***. For that reason, we included a control experiment in ***Chapter 2***, in which we specifically looked into the ventral visual processing stream. In this additional experiment, we controlled for visual confounds by only including stimuli that were matched in terms of visual information. This control experiment nuanced the results found with the subtraction paradigm, thereby indicating the importance of controlling for confounding factors. In ***Chapters 3 and 4***, we were not able to include a control experiment due to time constraints. However, as we focused on the neural activation at the whole brain level in those studies and did not specifically zoom in on the visual processes involved in arithmetic, the visual confound was less problematic in those studies.

Third, we used strict criteria for motion correction throughout this doctoral dissertation. Especially when scanning children, motion is an important confound to take into account, as excessive movement in the scanner induces undesirable noise in the neuroimaging data (Blumenthal, Zijdenbos, Molloy, & Giedd, 2002). Due to our rigorous rule of discarding runs in which participants moved more than one voxel size on two consecutive images, we lost a substantial number of runs in the studies in children (***Chapters 3 and 4***), which already had a rather small subject sample. However, the remaining data was qualitatively better and hence more powerful in detecting neural differences between conditions and between groups of subjects.

Fourth, the majority of research presented in this doctoral dissertation comprised imaging research in 9 to 12 year old children (***Chapters 3 and 4***). As suggested in Ernst, Rumsey and Munson (2003), we trained children before the scanning session using a mock scanner and limited the scanning time to 45 minutes to ensure data of sufficient quality, and to limit the amount of runs that had to be discarded due to motion criteria. Due to this time constraint, we were unable to collect any data from additional experiments to control for potential confounding factors (e.g., visual characteristics). We were also not able to acquire data from independent functional localizers that would have allowed us to perform more powerful univariate region of interest based analyses rather than the less powerful whole brain analyses we used now.

Similar to all previous neuroimaging studies in children with dyscalculia, we normalized the acquired functional scans to a standardized adult template. In the current studies and in Ashkenazi et al. (2012), Berteletti et al. (2014), Kucian et al. (2006) and Rosenberg-Lee et al. (2015) the children's brains were normalized to MNI space, in Davis et al. (2009) and De Smedt et al. (2011) to Talairach space. However, the use of an adult template for children's data is not without problems, as the brain structure of children is not the same as that of adults. Because there is no widely-used, standardized pediatric template available, caution is required when anatomically localizing specific focal regions in children based on region of interest software designed for adult brains. A more suitable alternative is to use independent functional localizers (see e.g., Berteletti et al., 2014; Prado et al., 2011), or to not look into focal regions in children but rather to investigate larger regions or use a whole-brain approach. We opted for the latter, given our inability to collect independent functional localizer scans due to time constrains.

Finally, we used rather strict selection criteria when recruiting the children with learning disorders (***Chapters 4 and 5***) in contrast to previous neuroimaging studies where rather lenient criteria were used. For example, in studies by Ashkenazi et al. (2012), Davis et al. (2009) and Rosenberg-Lee et al. (2015) children who scored below the 25th percentile on a standardized math test were categorized as having dyscalculia, and Berteletti et al. (2014) considered the 20 lowest scoring children out of 40 on two math tests as having mathematical deficits. This approach yields two disadvantages: using a 25th percentile cut-off is a large overestimation of the number of children with a learning disorder, and it is a categorization based on an administered test on one particular time point. However, children are not diagnosed with a specific learning disorder unless the deficits are present for at least six months, and persist despite targeted intervention (American Psychiatric Association, 2013). In this doctoral dissertation however, only children who had received a formal diagnosis set by an experienced clinician were included. Furthermore, these diagnoses were validated using data from a behavioral assessment, indicating that in fact the included children with dyscalculia showed impairments on arithmetic, and children with dyslexia on reading. Furthermore, the study described in ***Chapter 4*** was the first study to directly investigate the neural correlates of comorbid dyslexia/dyscalculia, rather than treating this comorbidity as a confound by either not taking reading ability into account in studies on dyscalculia (and vice versa for arithmetic ability in studies on dyslexia), or by discarding children with comorbid dyslexia/dyscalculia.

Throughout this doctoral dissertation, we have used a categorical approach towards the presence of learning disorders by categorizing children into groups. Alternatively, it is also possible to look at arithmetic ability and reading ability as continua, in which children with dyscalculia and dyslexia would be at the far left of the Gaussian distribution. This dimensional approach might address the fact that the cut-off to set a diagnosis is somewhat arbitrary: the best scoring children with dyscalculia will not differ from the worst scoring typically developing children. Furthermore, dyscalculia is a heterogeneous disorder, in which subtypes have been described (see e.g., Bartelet, Vaessen, Blomert, & Ansari, 2014) that are currently often not taken into account when using a categorical approach. An elaborate, dimensional approach that takes a broader range of cognitive variables that differentiate between subtypes of dyscalculia into account, might allow for a more detailed glance into dyscalculia (for the importance of thorough phenotyping, see also Lessov-Schlaggar, Rubin, & Schlaggar, 2016). However, a dimensional approach requires a larger subject sample to reach sufficient statistical power compared to a categorical approach, which is why we used the latter.

6.3 Future perspectives

Despite the novel findings presented in this doctoral dissertation, the neural correlates of arithmetic in adults and children with and without learning disorders are not yet fully understood. In this paragraph, we suggest a number of potentially fruitful directions for future neuroimaging research.

First, additional research is necessary to confirm the neural similarity of dyscalculia and dyslexia. Although our results clearly illustrated neural similarity between dyscalculia and dyslexia in both an arithmetic and a reading task, our tasks might not have been sensitive enough to pick up small effects specific to dyscalculia or dyslexia. In that respect, it would be interesting to measure the neural response of children with various learning disorders to a numerical magnitude processing task, as impairments in this process are thought to underlie arithmetic difficulties. However, as Fias, Menon and Szucs (2013) stated, it is unwarranted to focus merely on one specific component of dyscalculia, for example numerical magnitude processing, without taking other important components such as working memory or attention into account. Furthermore, as the results of our behavioral study indicated, domain-general processes (e.g., block design) might even be as informative, if not more informative, than domain-specific processes (e.g., numerical magnitude processing). We deliberately chose to focus on the key behavioral deficit associated with dyscalculia (i.e., arithmetic) in the design of the imaging paradigm, as it provides us with a first, general indication of the specificity of the neural correlates of arithmetic in two groups of children with distinct cognitive profiles, yet that both suffer from impairments in arithmetic. However, future studies could benefit from using tasks that tap into more specific processes, both domain-specific and domain-general.

Second, in the context of this doctoral dissertation we only focused on task-related neural activation using fMRI. However, other neural markers might provide different novel insights into the apparent neural similarity of dyscalculia and dyslexia as well. In particular, it would be interesting to also look into (dis)similarities in functional and structural connectivity between children with dyscalculia and children with dyslexia. Previous research has reported hyper-connectivity between frontal and parietal areas in children with dyscalculia in the context of arithmetic (Jolles et al., 2016; Rosenberg-Lee et al., 2015), yet no study has currently looked into functional connectivity during arithmetic in children with dyslexia. Regarding structural connectivity, a DTI study by Rykhlevskaia, Uddin, Kondos and Menon

(2009) found reduced FA values in the right temporoparietal cortex in children with dyscalculia, and lower FA values have been reported in the left temporoparietal and frontal areas in children with dyslexia (see Vandermosten, Boets, Wouters, & Ghesquière, 2012 for a review). A direct comparison of functional and structural connectivity between children with learning disorders however, has not yet been made and represents an area for future research.

Third, it is currently unclear how the neural similarity between dyscalculia and dyslexia emerges: It is possible that the neurobiological origin of both learning disorders is already similar before formal education, and remains stable, hence similar, throughout formal schooling. However, it is also possible that the degree of neural similarity is dependent on the developmental or educational phase that children are in. To address these outstanding questions, we suggest a longitudinal study, in which the neural correlates of arithmetic are investigated from before formal arithmetic instruction (i.e., kindergarten), through the early arithmetic stages in which children are in the process of learning how to solve arithmetic problems (i.e., Grade 2), until children are *accomplished* in solving basic arithmetic problems, similar to the children included in this doctoral dissertation (i.e., Grade 4 to 6). Although this is a very ambitious project practically speaking, it would allow to investigate the development of the neural correlates of arithmetic throughout formal schooling. Even more ambitious would be to recruit both kindergartners at risk for developing learning disorders, as well as low-risk kindergartners. Using a retrospective approach it would then be possible to, depending on which children were diagnosed with a learning disorder in a later stage, look back at potential (neural) differences in kindergarten between children with and children without a learning disorder. Family risk studies are non-existing in dyscalculia, despite the reported heritability of dyscalculia (Alarcón, DeFries, Light, & Pennington, 1997). On the other hand, they are frequently used in the context of dyslexia, where a recent meta-analysis showed that the average prevalence of dyslexia in children with a family risk is around 45% (Snowling & Melby-Lervåg, 2016). This type of design would allow us to gain a unique and in depth insight into the development of the neural correlates of arithmetic in children with and without specific learning disorders.

Finally, the studies included in this doctoral dissertation were all performed in participants in Flanders who had all received formal schooling in the Flemish educational system. The math curriculum in Flanders is rather focused on automatizing arithmetic facts, as children from a young age onwards are instructed to retrieve results to arithmetic problems, rather than to count. However, this emphasis on automatization is not a world-wide phenomenon; In Canada, for example, children are authorized to use counting strategies to solve arithmetic problems (Campbell & Xue, 2001). The neural correlates of this difference in mathematical instruction remains unclear to date, and could be investigated using a cross-cultural design. Furthermore, this type of study might be of particular interest for children with dyscalculia and dyslexia having difficulties automatizing arithmetic facts, and might point towards alternative remedial programs or mathematical instruction for children with learning disorders.

Collectively, we believe that these suggestions will contribute to the current literature, and will provide us with new insights into the (neurobiological) origin of dyscalculia, and of learning disorders in general. Only by means of combining methods, behavioral and neuroimaging (functional and structural), cross-sectional, longitudinal and cross-cultural, and by gaining theoretical knowledge on the underlying cognitive and neurobiological origin of dyscalculia and dyslexia, can we attempt to create better future perspectives for children with learning disorders.

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